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TUMORS OF THE MALE SEX ORGANS

Frank J. Dixon, M.D.
and
Robert A. Moore, M.D.

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TUMORS OF THE MALE SEX ORGANS

Frank J. Dixon, M.D.
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ARMED FORCES INSTITUTE OF PATHOLOGY

ATLAS OF TUMOR PATHOLOGY

Section VIII—Fascicles 31b and 32

TUMORS OF THE MALE SEX ORGANS

by

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ATLAS OF TUMOR PATHOLOGY

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Frank J. Dixon
Robert A. Moore

TUMORS OF THE MALE SEX ORGANS

TABLE OF CONTENTS

Page No.

TUMORS OF THE PROSTATE 7
Introduction 7
Figs. 1, 2
Adenocarcinoma 10
Figs. 3–22
Epidermoid Carcinoma 37
Figs. 23, 24
Sarcoma of the Prostate and Neck of the Vesicle 40
Figs. 25–28
Tumor-like Lesions of the Prostate 41
Figs. 29, 30
TUMORS OF THE TESTIS 48
Introduction 48
Classification 50
Fig. 31
Comparison of Testicular and Ovarian Tumors 53
Incidence 53
Germinal Tumors 55
Tumor Group I—Seminoma, Pure 57
Figs. 32–43
Tumor Group II—Embryonal Carcinoma, Pure or with Seminoma 72
Figs. 44–59
Tumor Group III—Teratoma, Pure or with Seminoma 90
Figs. 60–68
Tumor Group IV—Teratoma with either Embryonal Carcinoma or Choriocarcinoma or Both and with or without Seminoma 100
Tumor Group V—Choriocarcinoma, Pure or with either Seminoma or Embryonal Carcinoma or Both 101
Figs. 69–71
Nongerminal Tumors 104
Figs. 72–87
Interstitial Cell Tumors 104
Figs. 79–83
Androblastomas 120
Figs. 84–87

Page No.

TUMORS OF THE TESTICULAR APPENDAGES—EPIDIDYMIS, SPERMATIC CORD, AND TESTICULAR TUNICS 127
Introduction 127
Adenomatoid Tumors 127
Figs. 88–98
Benign Connective Tissue Tumors 136
Figs. 99–101
Sarcomas 138
Figs. 102–104
TUMORS OF THE URETHRA (Originally planned as Fascicle 31b) 143
Introduction 143
Papilloma 143
Figs. 105–107
Carcinoma 143
Figs. 108–111
Sarcoma 147
Tumor-like Lesions 147
TUMORS OF COWPER'S GLANDS 150
Figs. 112–114
TUMORS OF THE SEMINAL VESICLES 154
Introduction 154
Carcinoma of the Seminal Vesicles 154
TUMORS OF THE PENIS 156
Introduction 156
Premalignant Lesions and Preinvasive Carcinoma 156
Figs. 115–120
Epidermoid Carcinoma 158
Figs. 121–125
Miscellaneous Malignant Tumors 167
Tumor-like Lesions 167
Fig. 126
TUMORS OF THE SCROTUM 170
Introduction 170
Epidermoid Carcinoma 170
Figs. 127–130
Miscellaneous Tumors 173
Figs. 131–135.

TUMORS OF THE MALE SEX ORGANS

TUMORS OF THE PROSTATE

Introduction

The prostate gland is formed in embryonic life by a number of evaginations from the posterior and lateral walls of the posterior urethra. The male prostate is divided into five lobes: the posterior lobe, which is posterior to the urethra and the deferential canal; the middle lobe, which lies between the urethra and the deferential canal; the two lateral lobes, the glands of which empty into the sides of the verumontanum; and the anterior lobe, a vestigial structure represented by from eight to ten acini anterior to the urethra (fig. 1). The ejaculatory ducts pass downward and forward between the middle and posterior lobes. In the female the prostate remains vestigial. It corresponds only to the lateral and middle lobes of the male prostate and lacks a posterior lobe. This fact is of interest in relation to nodular hyperplasia and prostatic carcinoma. The former involves only the ambisexual part of the male prostate, while the latter is predominantly a disease of the posterior lobe, or purely male part of the prostate.

From 15 to 30 branching tubular glands imbedded in connective tissue stroma make up the male prostate (fig. 2). The glandular epithelium consists of two layers: tall columnar, luminal cells and flattened or cuboidal basal cells. The epithelium rests on a narrow (7 to 10 microns), homogeneous, collagen-like basement membrane. The stroma consists of approximately equal amounts of smooth muscle and fibrous tissue.

The normal development and maintenance of the prostate, as well as of other male secondary sexual organs, is dependent upon endocrine stimulation by the testes. In castrates, both human and animal, the prostate atrophies quickly. The endocrine function of the testes is in turn dependent upon gonadotropic hormone from the pituitary, and absence of the pituitary hormone also results in prostatic atrophy.

Senile atrophy of the prostate usually begins near the end of the fourth decade simultaneously with a decreased androgen excretion in the urine. Morphologic manifestations of atrophy include irregularities in character of the epithelium, loss of secretory activity by glandular epithelium, complete atrophy of acini, and atrophy of smooth muscle of the stroma with replacement by fibrous tissues (Moore, 1942).

If nodular hyperplasia of the prostate is considered non-neoplastic, then almost all prostatic tumors may be classified as malignant. Adenocarcinoma is by far the most common tumor. The remainder are epidermoid carcinomas,

Figure 1.* Anatomic sketch of prostate. Upper is transverse section at level of colliculus seminalis and lower is sagittal section. A: Posterior lobe; B: Middle lobe; C: Anterior lobe; and D: Lateral lobes. Note position of posterior lobe, inferior and posterior to ejaculatory ducts. A. F. I. P. Acc. No. 218716–21.

Figure 2.* Transverse section of normal prostate at level of colliculus seminalis showing general glandular pattern and ejaculatory ducts. A. F. I. P. Acc. No. 218716–22.

*From Moore, R. A. The evolution and involution of the prostate gland. Am. J. Path., 12: 599–624, 1936.

Fig. 1

Fig. 2

probably arising from urethral mucosa, and sarcomas of the prostate and tissues of the neck of the vesicle.

Adenocarcinoma

SYNONYMS AND RELATED TERMS: Acinar carcinoma; alveolar adenocarcinoma; alveolar carcinoma; alveolar cell carcinoma; carcinoma; carcinoma simplex; cylindrical (duct) cell carcinoma; glandular carcinoma; small cell carcinoma.

DEFINITION. A malignant tumor which arises from the acinic and/or ductal epithelium of the prostate and which may vary considerably in its glandular differentiation and anaplasia.

TYPES. From a clinico-pathologic point of view, carcinoma of the prostate can be divided roughly into three types. The first type is **clinically manifest** and usually has presenting symptoms characterized by local pain and urinary abnormalities, both of which may be intensified late in the disease. The prostate is enlarged. The normal contours of the prostate are destroyed. Local tumor invasion is common, but metastases are late. These tumors are usually well differentiated adenocarcinomas. The second type, **occult carcinoma,** is characterized by metastases widespread from a small, unsuspected primary growth. There is a paucity of local symptoms with little, if any, prostatic enlargement and no change in prostatic contour. Frequently the presenting symptoms are related to metastases. The histologic structure is usually anaplastic adenocarcinoma or carcinoma simplex. The third group, the **latent carcinomas,** are small, asymptomatic tumors which do not metastasize. These tumors are found usually at autopsy, occasionally in surgical specimens. Although their significance is not apparent, they probably represent small carcinomas which would have developed into clinically manifest tumors if the patients had lived. These latent tumors support the opinion that carcinoma of the prostate develops slowly over a long period of years.

INCIDENCE. Prostatic carcinoma is a common neoplasm of men, extremely rare before the age of 40, but increasing in incidence each decade thereafter. Careful studies of large series of unselected autopsy material place the incidence of carcinoma of the prostate in all men over 40 at about 20 percent. The frequency increases from 10 to 17 percent in the fifth decade to 29 to 39 percent in the ninth decade. Incidence established from autopsy material is much higher than that based on clinical diagnoses because of the large number of latent tumors. Calculations based on the unselected autopsy series of Moore (1935) and of Rich, in which 104 prostatic carcinomas were found in 667 autopsies, would indicate that latent carcinomas of the prostate outnumber those clinically manifest about four to one.

Gordon's survey of hospitalized cancer patients in the United States showed that cancer of the prostate made up 10 percent of the cases of cancers in males and accounted for 11.5 percent of all male cancer deaths. The peak

incidence of prostatic carcinoma is in the seventh decade, with approximately three fourths of the deaths in the seventh and eighth decades.

Carcinoma of the prostate has the same incidence in Europe as in the United States, but in China it is a rare disease. Hu and Ch'in found only one prostatic carcinoma in 379 carcinomas in men autopsied in the hospital of the Peiping Union Medical College.

ETIOLOGY. Because carcinoma of the prostate is so distinctly a disease of elderly men, its etiology and histogenesis probably depend upon some previous alteration incident to the aging process. After the age of 40 there is a gradual decrease in the biochemically active urinary androgens simultaneous with atrophy of the prostatic glands, most evident in the posterior lobe. It is in these atrophic glands that almost all of the carcinomas arise, with apparent derivation of malignant cells from atrophic. Fifty out of 52 tumors small enough to allow determination of their points of origin arose from atrophic glands (Moore, 1935). Because atrophy is most marked in the posterior lobe, it is not surprising that the great majority of tumors arise there.

The difference in behavior of the posterior lobe of the prostate and the remaining prostatic tissue is explained by the fact that the former, a distinctly male structure, undergoes atrophy with decrease in the androgen level, while the ambisexual lateral and middle lobes often fail to atrophy and instead participate in nodular hyperplasia, so frequently seen in males past middle age.

There is no causal relationship between nodular hyperplasia of the prostate and carcinoma. Because both lesions are common in older men, they frequently coexist, but the incidence of nodular hyperplasia in tumor-bearing and tumor-free prostates is the same. In addition, the two lesions are rarely morphologically related, because carcinoma usually arises in the posterior lobe of the prostate, which never participates in nodular hyperplasia. When carcinoma does arise in hyperplastic lateral lobes, the two lesions—i.e., carcinoma and hyperplasia—are usually discrete (fig. 6).

COURSE AND TREATMENT. The course of untreated, clinically manifest carcinoma of the prostate is relatively rapid. In a series of 1,000 cases reviewed some 20 years ago by Bumpus, more than one half of the tumors metastasized within a year after onset of symptoms. The average duration of life from onset of symptoms was 31 months. Two thirds of the patients who presented metastases died within nine months and those without metastases lived an average of 12 months. Death most frequently resulted from urinary complications secondary to urethral obstruction.

Present day therapy has improved the hopeless outlook reflected by the above figures. For the small group of patients (approximately five percent) whose tumors are sufficiently localized to allow complete excision, radical

perineal prostatectomy offers a better than 50 percent chance of a 5-year survival. In the hands of the leading proponent of this procedure, H. H. Young, radical resection carried a mortality of only about seven percent. Because carcinomas of the prostate almost always arise in the subcapsular region and are usually found in the posterior lobe, any operation short of radical perineal prostatectomy can only be a palliative procedure.

For the remaining 95 percent of the patients in whom the tumor has either metastasized or extended far enough to make complete resection impossible, androgen control offers definite temporary relief and a significant prolongation of life. The growth of both normal and, in most cases, malignant prostatic epithelium is dependent on androgen stimulation. Either the removal of the source of androgens by orchiectomy or the inhibition or neutralization of androgenic stimulus by administration of estrogens produces an adverse effect on the tumor (figs. 18, 19). With either of the above methods or with a combination of the two, 80 percent of patients show symptomatic relief and clinical improvement. In an appreciable number, the tumor becomes smaller. Intestinal obstruction, urinary obstruction, and even transverse myelitis secondary to tumor growth have in some instances disappeared completely as a result of androgen control (Ackerman and Regato). Usually, however, after a period of months (or, less frequently, years) tumors in patients improved by androgen control begin to grow again, and neither intensification nor change in type of androgen control is effective. The previously sensitive tumor cells eventually become independent of the effect of androgens and perhaps are then similar to the 20 percent of tumors originally insensitive to androgen control. The administration of estrogen may cause certain undesirable side effects such as gynecomastia, dependent edema, and testicular atrophy. The development of these changes has no correlation with the response of the tumor to treatment (Wattenberg and Rose).

Recent reports indicate that survival rates of patients treated by androgen control are significantly higher than rates for both those untreated and those treated merely to relieve urinary obstruction. A more exact statement of the prognosis with androgen control awaits the reports of larger follow-up series.

CYTOLOGIC DIAGNOSIS. The identification of cancer cells in expressed secretion of the prostate may be helpful in confirming the diagnosis of carcinoma.

CARCINOMA OF THE PROSTATE IN ANIMALS. In sharp contrast to its frequent occurrence in man, carcinoma of the prostate is apparently rare in animals. In dogs carcinoma of the prostate comprises only from one to two percent of all tumors, and in other species the incidence is even lower. Adequate study of canine material has failed to find any latent carcinomas of the prostate in old dogs, a significant observation in view of the 20 percent incidence of such tumors in human males over 40 years.

Experimental attempts to produce adenocarcinoma of the prostate in animals have been uniformly unsuccessful. In contrast to the known stimulating effects of androgens on human prostatic carcinoma, androgen administration to animals has not produced prostatic tumors. However, in animals as in men, prolonged administration of estrogens results in a squamous metaplasia of prostatic epithelium (fig. 17) but not in neoplasia. By injection of benzypyrene directly into animal prostates, Moore and Melchionna produced after 110 days epidermoid carcinomas and leiomyosarcomas but not adenocarcinoma.

BIOCHEMISTRY. Of special interest in carcinoma of the prostate are the acid and alkaline phosphatases. These enzymes hydrolyze phosphoric esters, the acid form operating optimally at pH 5 and the alkaline at approximately pH 9. The enzymes are analyzed in vitro by measurement of the rate at which they liberate phosphoric acid from phosphoric esters. Acid phosphatase is produced only by adult prostatic epithelium and its malignant variant (Gutman, Sproul, and Gutman). Alkaline phophatases are found in many places in the body. The alkaline phosphatase of bone is frequently altered by osseous metastases of prostatic carcinoma.

Acid phosphatase is normally formed by prostatic epithelium and eliminated with prostatic secretions. In prostatic carcinoma, however, the acid phosphatase presumably formed by metastasizing tumor cells finds its way into the blood stream, elevating the serum acid phosphatase. When carcinoma of the prostate is absent or contained within the vicinity of the prostate, the serum acid phosphatase level does not exceed three King Armstrong (KA) units. In 85 percent of prostatic carcinomas with metastases, the serum acid phosphatase is elevated. In 50 percent the elevation is 10 KA units or more. An elevation of serum acid phosphatase to 10 KA units or more is an absolute indication of metastatic prostatic carcinoma (Gutman, Gutman, and Robinson).

The osseous metastases of prostatic carcinoma frequently stimulate bone formation, and in approximately 85 percent of patients with osseous metastases, the serum alkaline phosphatase is also elevated. This elevation, however, is not specific for prostatic carcinoma, in contrast with the serum acid phosphatase elevation.

The metabolic activity and acid phosphatase production of both malignant and normal prostatic epithelium are dependent upon androgenic stimulation. The elevated serum acid phosphatase level in prostatic carcinoma is further raised by the administration of androgens, while it is reduced in from 80 to 90 percent of patients by orchiectomy or estrogen administration. The variability in the drop of serum acid phosphatase following androgen control therapy apparently depends upon the variability in the degree to which different tumors depend upon androgen (Huggins and Hodges).

Figure 3. Carcinoma of prostate. Tumor can be seen as poorly defined subcapsular white area in right lateral portion of posterior lobe. A. F. I. P. Acc. No. 218716–23.

Figure 4. Advanced carcinoma of prostate. White tumor tissue occupies most of the posterior lobe and left lateral lobe. There is capsular invasion in left lateral posterior sector, and irregular extension into middle lobe and right lateral lobe. Note intact posterior capsule, which is rarely invaded by tumor. Urethra is uninvolved, as is usual until late in the course of the disease. (From Moore, R. A. A Textbook of Pathology. Philadelphia: W. B. Saunders Co., 1951.) A. F. I P. Acc. No. 218716–24.

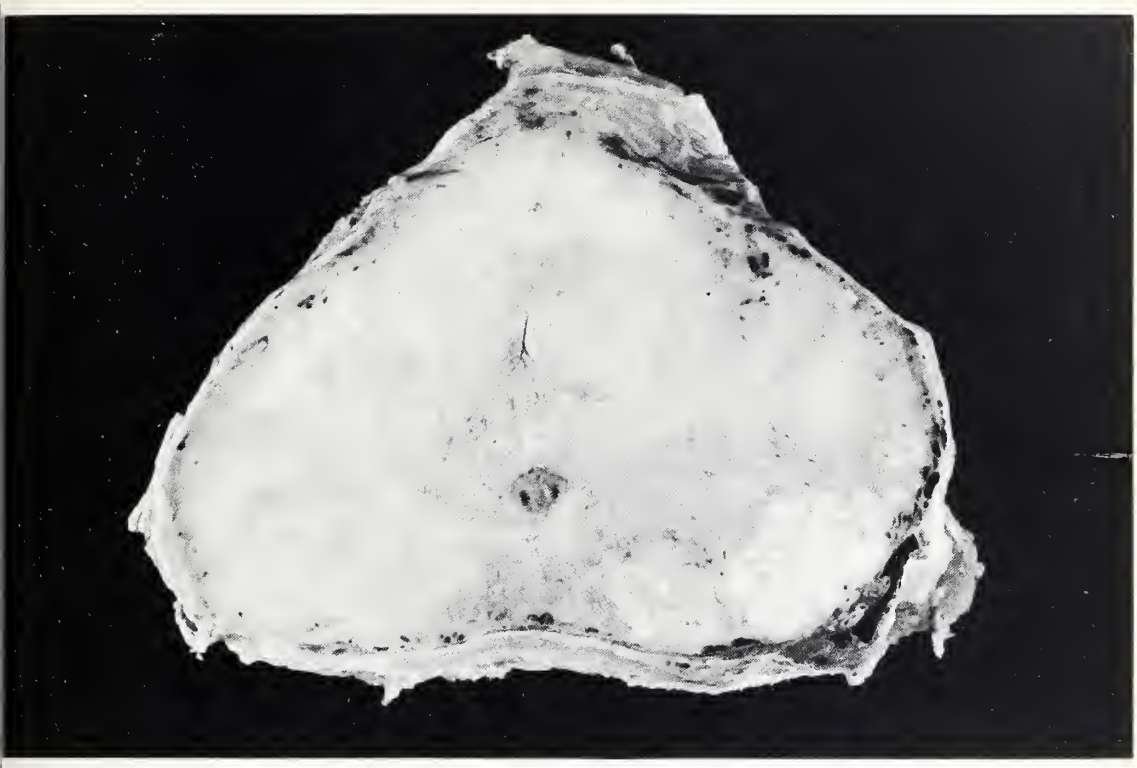

Fig. 3

Fig. 4

In those patients showing a favorable response to orchiectomy, there is a return of elevated serum acid phosphatase to normal or near normal limits within 24 to 48 hours. It remains at normal for the duration of the remission, usually a matter of months, and rises again as tumor growth is resumed. There is also an immediate increase in the serum alkaline phosphatase following orchiectomy, which indicates osteoblastic activity presumably in the region of osseous metastases. This activity gradually declines, reaching normal in from three to four months. Administration of estrogens produces changes in acid and alkaline phosphatase levels similar to, but more gradual in their development than, those caused by orchiectomy.

GROSS. Between one half and three fourths of all prostatic carcinomas arise in the posterior lobe. The middle lobe is rarely involved. Of 66 carcinomas with known origins, 76 percent arose in the posterior lobe, 9 percent in the lateral lobes, 15 percent in the anterior lobe, and none in the middle lobe (Moore, 1935). According to Gaynor, over 95 percent of all prostatic carcinomas are located in the subcapsular region. Multicentric origin is reported in from 10 to 20 percent.

The size of prostatic carcinomas varies from microscopic proportions to entire replacement and moderate enlargement of the prostate by neoplasm (figs. 3, 4). There is no correlation between the size of the prostate and the presence of tumor. Gross identification of carcinoma of the prostate, especially the small latent forms, is difficult and often impossible, as is indicated by the frequency of histologically demonstrable carcinomas in unsuspected routine autopsy sections. The tumors grossly discernible are usually at least five mm. in diameter. They are irregular in outline, usually in contact with the capsule, and not sharply demarcated from the surrounding tissue. About half the carcinomas have a distinct yellow flecking, are firm, and may be granular on cut surface. The remainder are gray to white, homogeneous or slightly fibrillar, and hard. There are two lesions which may be confused upon gross examination with carcinoma: focal atrophy and hyperplastic tuberculosis. In the former, the atrophic area is also firm, irregular, and not sharply delimited but identifiable by its bluish white, translucent appearance. The tuberculous lesion (fig. 5) has a yellow-white color closely resembling that of carcinoma, but usually has a moderately sharp, scalloped border and is relatively soft (Moore, 1935).

Gross invasion of the prostatic capsule is not unusual. However, in spite of frequent early invasion both of lymphatics within the prostate (fig. 13) and of the prostatic capsule, invasion of adjacent structures is late and relatively uncommon. Posteriorly, in the region of Denonvilliers' fascia, the capsule is especially resistant to tumor extension (fig. 4). This accounts for the extremely rare invasion of the rectum by prostatic carcinoma (1.5 percent—Young).

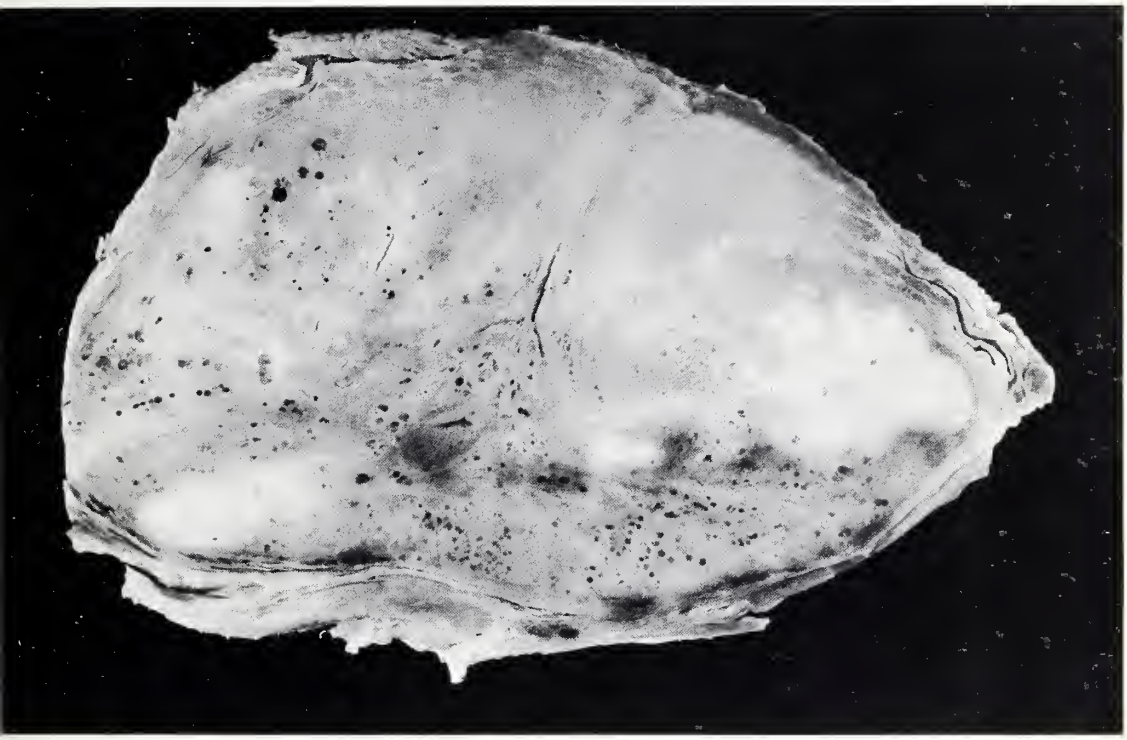

Figure 5. Tuberculosis of prostate involving primarily the right lateral lobe. The tuberculous lesion has the white color of carcinoma, but may be distinguished from the latter by its sharp scalloped border and soft texture. (From Moore, R. A. Tuberculosis of the prostate gland. J. Urol., 37: 372–384, 1937.) A. F. I. P. Acc. No. 218716–25.

In any one tumor, the extension is clearly in a definite direction. With a primary focus in the posterior lobe there is early spread in a cephalocaudad direction just beneath the capsule. This extension rarely crosses the midline. In an anterior lobe lesion, however, spread is directed laterally and crosses the midline. The anterior lobe tumors are less invasive than those of the posterior lobe. A lesion in the lateral lobe extends laterally to the capsule and then behaves as a posterior lobe tumor (Moore, 1935).

Late extension of prostatic carcinoma to the bladder in 44 percent of autopsy cases and to seminal vesicles in 18 percent has been reported by Arnheim. Perivesical and perirectal tissues are occasionally involved and rectum and urethra only rarely.

MICROSCOPIC. Since the diagnosis of carcinoma of the prostate is frequently based on a microscopic finding, with no gross or clinical evidence of a tumor, it is of great importance that the microscopic criteria for carcinoma be clearly understood by all pathologists.

Microscopic grading of prostatic carcinomas may give an indication of prognosis (Muir). Division of adenocarcinoma of the prostate into four histologic grades of ascending malignancy results in a distribution as follows: Grade I—19 percent, Grade II—50 percent, Grade III—27.5 percent, and Grade IV—3.5 percent (Kahler). The term adenocarcinoma has been used to describe the majority of those tumors which are relatively well differentiated (figs. 7–11). Carcinoma simplex and small cell carcinoma refer to varieties of the less common, undifferentiated tumors (fig. 12). A rare but striking type is the lipoid-rich carcinoma, which grossly is yellow and microscopically is composed of large, vacuolated, lipoid-containing cells.

The well differentiated tumors, especially small ones, present a diagnostic problem because the degree of anaplasia is slight. The malignant cells are low columnar to cuboidal with definite cell walls and relatively dense, acidophilic cytoplasm. The nuclei are slightly larger in relation to the cell than normal nuclei and show some variation in staining power and morphology. The cells are oriented and arranged in definite acini, which differ from the normal only in their smaller size and lack of papillae. The acini usually contain some secretion but rarely, if ever, corpora amylacea.

The malignant nature of these small acini may be recognized by their relation to the surrounding stroma. In the normal prostate the acini are invested by a narrow band of pure collagenous connective tissue. This zone follows all irregularities of the acini and is devoid of capillaries. In nodular hyperplasia this relationship is preserved. However, in the earliest degrees of neoplasia there is a beginning loss of this limiting zone, and the acini are arranged without regard for the regular whorls of smooth muscle, connective tissue, and elastic membranes (figs. 6–11). Further evidence of invasion is the presence of epithelial cells and acini within the perineural lymphatic

spaces (Moore, 1935) (fig. 13). Such perineural lymphatic invasion is found in from 80 to 90 percent of prostatic carcinomas. It is more common in tumors of high grade malignancy and in tumors which originate just beneath the capsule.

Because almost all carcinomas of the prostate originate in zones of glandular atrophy, the differentiation of atrophic glands from neoplastic glands is important. Although frequently collapsed, atrophic glands are larger than neoplastic and are lined with small, regular, cuboidal cells with uniform nuclei which are usually smaller, darker, and more regular than those of malignant cells. The atrophic glands are surrounded by a thickened, collagenous, limiting membrane and oriented to the smooth muscle bundles of the stroma.

The metaplastic transitional and squamous prostatic epithelium found in or near zones of infarction must also be differentiated from carcinoma (figs. 14–16). These epithelial islands are most often found associated with infarcts in nodular hyperplasia and are easily recognized when adjacent to necrotic, infarcted tissue. After the infarct has healed, the metaplastic epithelium may persist, and the lesion can then best be recognized by the complete absence of smooth muscle in the healed infarct. A differential stain shows only dense connective tissue and islands of metaplastic epithelium; the absence of invasion can be established by the presence of a typical collagenous limiting membrane about each island.

Finally, atypical hyperplasia of the prostatic epithelium must be differentiated from carcinoma. In the former condition the acini are somewhat larger than those in carcinoma and are surrounded by the normal limiting membrane. The epithelial cells are taller, sometimes forming a double layer, and the nuclei are smaller and more basal in position.

Following androgen control therapy, a minority of tumors show histologic changes in the tumor cells (figs. 18, 19). These changes are greater with estrogen administration than after orchiectomy. In both cases there are reduction in size of nuclei up to 50 percent, condensation of chromatin, loss of nucleoli, cessation of mitoses, and finally pyknosis. In the cytoplasm there is first an appearance of basal vacuoles which enlarge and, after rupture of cell membranes, coalesce with vacuoles of adjacent cells. Finally, the pyknotic nuclei lie free in clear acinic spaces (Schenken, Burns, and Kahle). Controlled preservation and fixation of before-and-after-treatment specimens, especially when the latter are from autopsy material, are of utmost importance in determining significant cytologic changes in the tumor.

The administration of estrogen in the male also produces histologic changes in the derivatives and vestiges of the müllerian duct system and in the breast. The epithelium of the prostatic urethra and utricle, which is homologous to vaginal mucosa, undergoes hyperplasia, which results in

Figure 6. Relatively rare occurrence of carcinoma of the prostate originating in nodule of hyperplasia. Hyperplastic nodule is for the most part circumscribed by characteristic encircling glands. Carcinoma is ovoid nodule of small, closely packed glands, among which a few large hyperplastic glands are still visible. A. F. I. P. Acc. No. 218716–26.

Figure 7. Diffuse infiltration by well differentiated adenocarcinoma. Carcinomatous acini show characteristic complete lack of orientation. A few large nonmalignant glands and ducts and a single corpus amylaceum can be seen. × 45. (From the Armed Forces Institute of Pathology.) A. F. I. P. Acc. No. 144985–2.

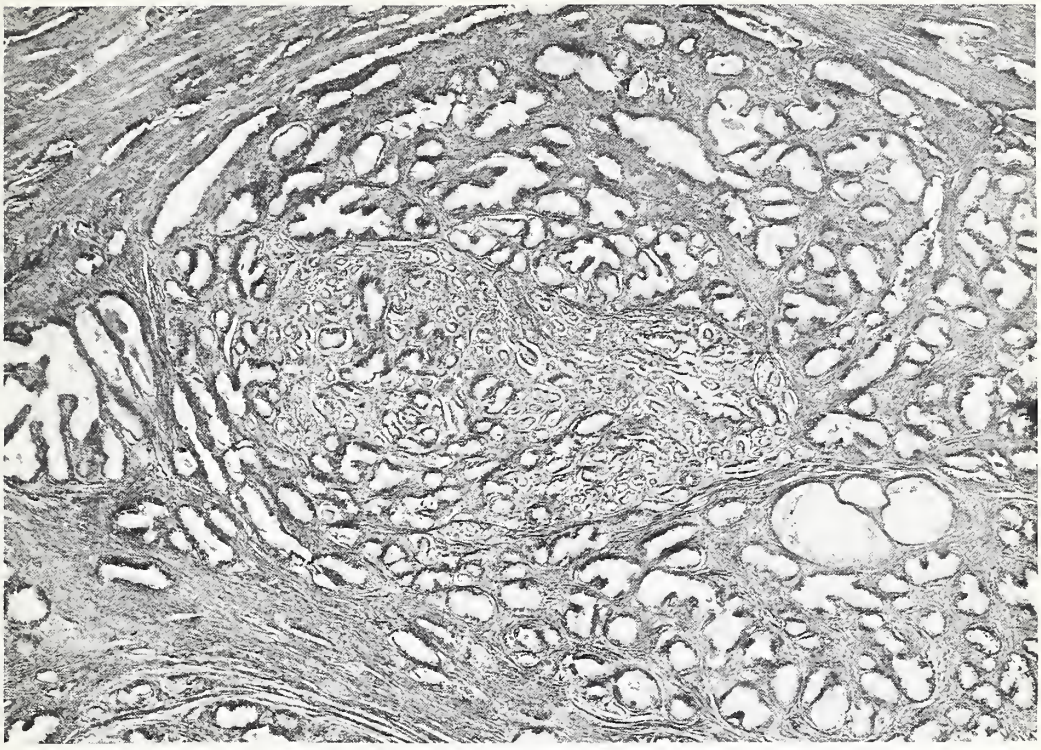

Fig. 6

Fig. 7

Figure 8* Well differentiated columnar cell adenocarcinoma of prostate showing closely packed disoriented glands. × 185. A. F. I. P. Acc. No. 144985–1.

Figure 9.* High power of tumor seen in figures 7 and 8. Note great regularity of glandular epithelium, basal nuclei, and presence of small amount of secretion. Best indication of malignancy at this power is the lack of basement membrane encircling each gland. × 435. A. F. I. P. Acc. No. 144985–3.

*From the Armed Forces Institute of Pathology.

Fig. 8

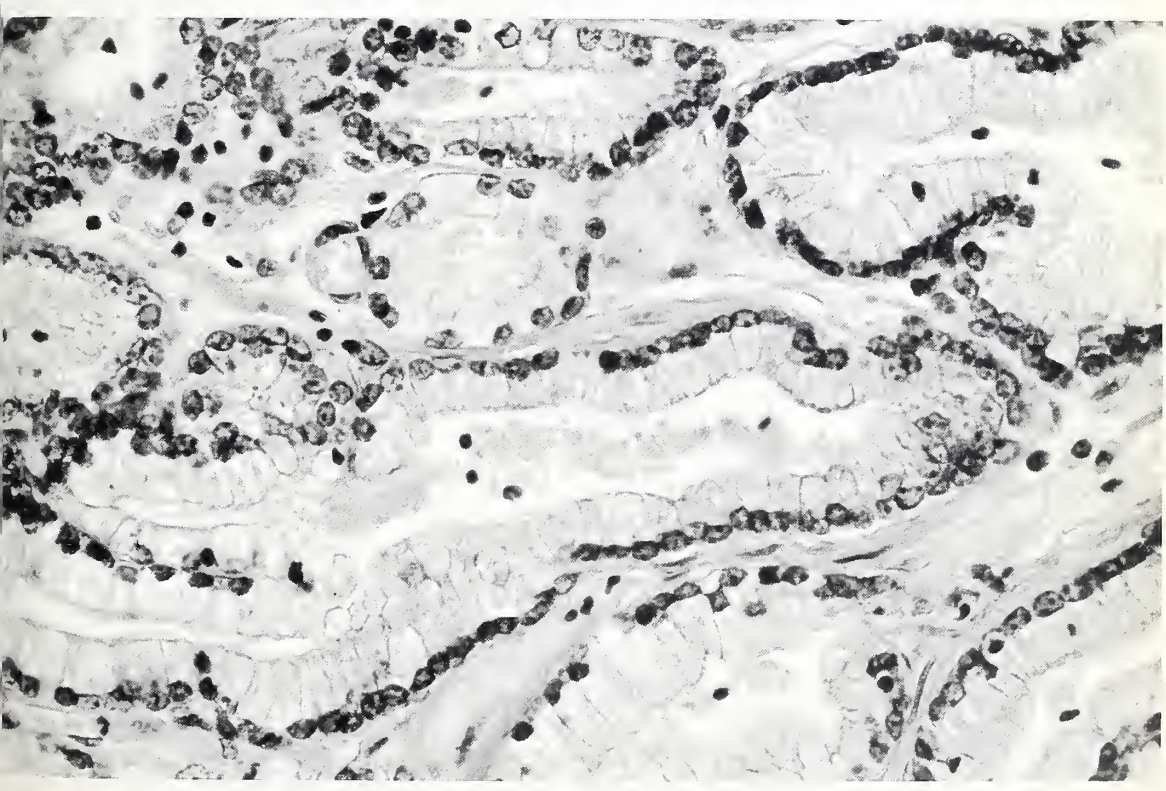

Fig. 9

Figure 10. Moderately undifferentiated, anaplastic adenocarcinoma of prostate. Acini vary considerably in size and are completely without orientation. There is extensive infiltration of stroma by small clumps of cells and even by single tumor cells. Papillary tumor growth can be seen in large acini. × 185. A. F. I. P. Acc. No. 218716–11.

Figure 11. High power view of tumor seen in figure 10. Detail of tumor cells and extensive invasion can be seen. Single tumor cells are found in stroma. Again lack of limiting basement membrane about glands is obvious. × 355. A. F. I. P. Acc. No. 218716–10.

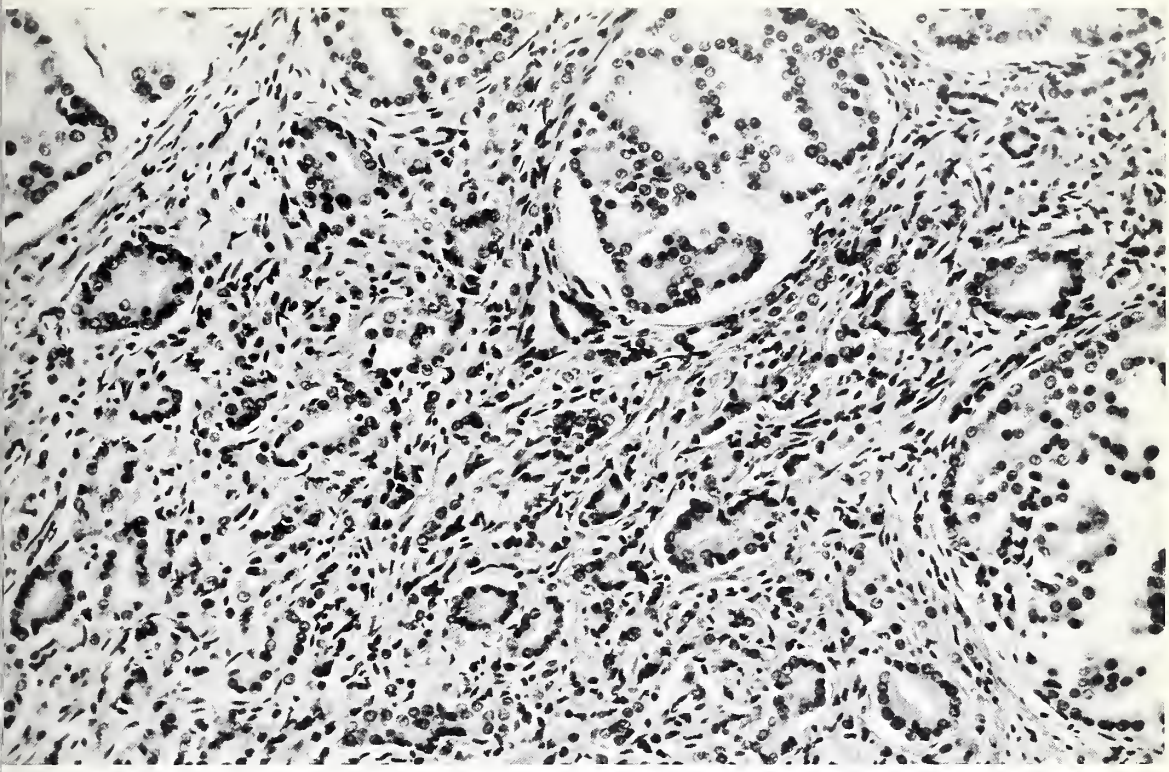

Fig. 10

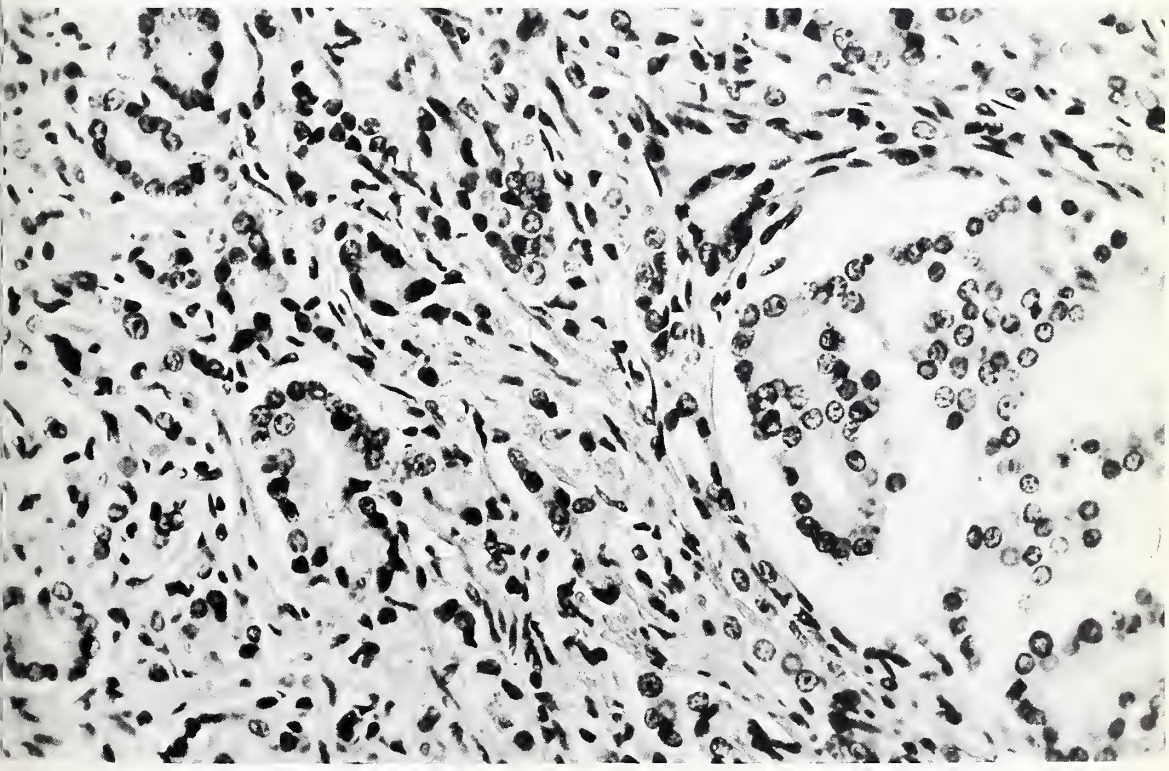

Fig. 11

Figure 12. Completely undifferentiated carcinoma of prostate. No well defined acini are visible. The tumor cells grow in solid sheets and display frequent mitoses. Large nuclei, prominent nucleoli, and variation in cell size are in marked contrast to the lack of atypical cells in the more characteristic prostatic carcinomas. × 475. A. F. I. P. Acc. No. 218716–13.

Figure 13. Perineural lymphatic invasion by prostatic adenocarcinoma. Nerve is visible in center of large ring of malignant acini. This rather common finding in prostatic carcinoma is often the best microscopic evidence of malignancy. It is presumably the cause of much of the pain associated with these tumors. × 475. A. F. I. P. Acc. No. 218716–9.

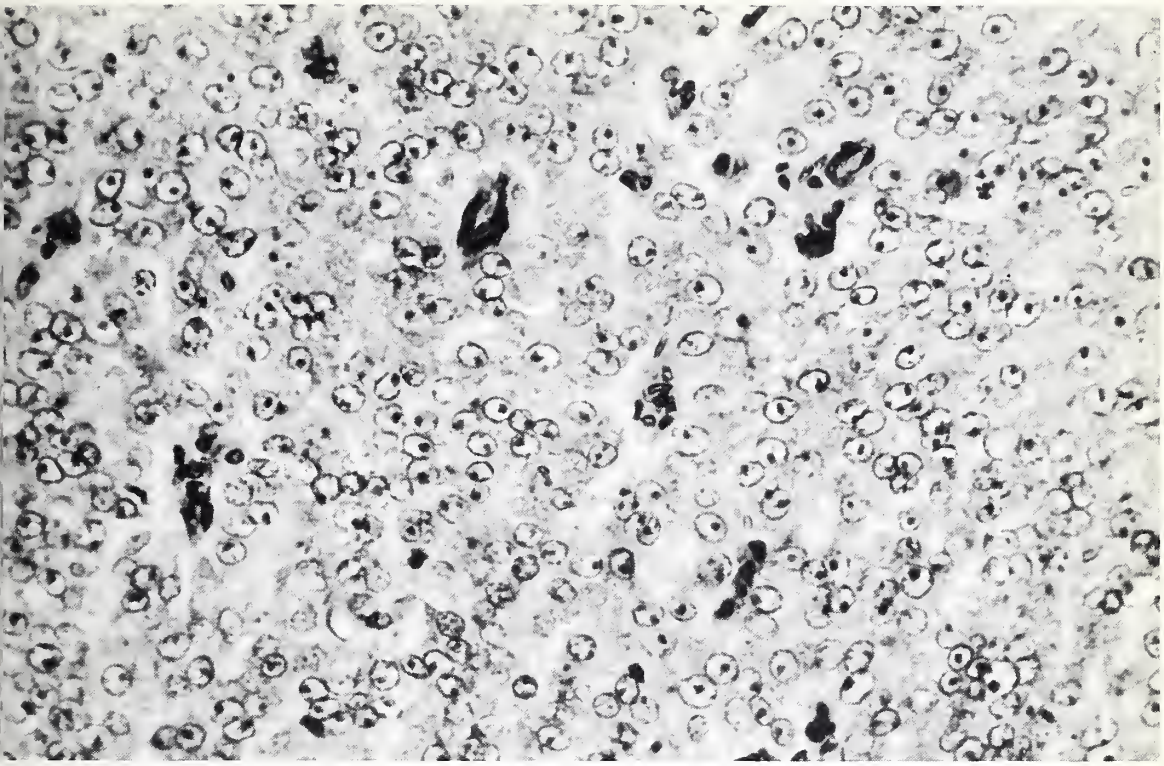

Fig. 12

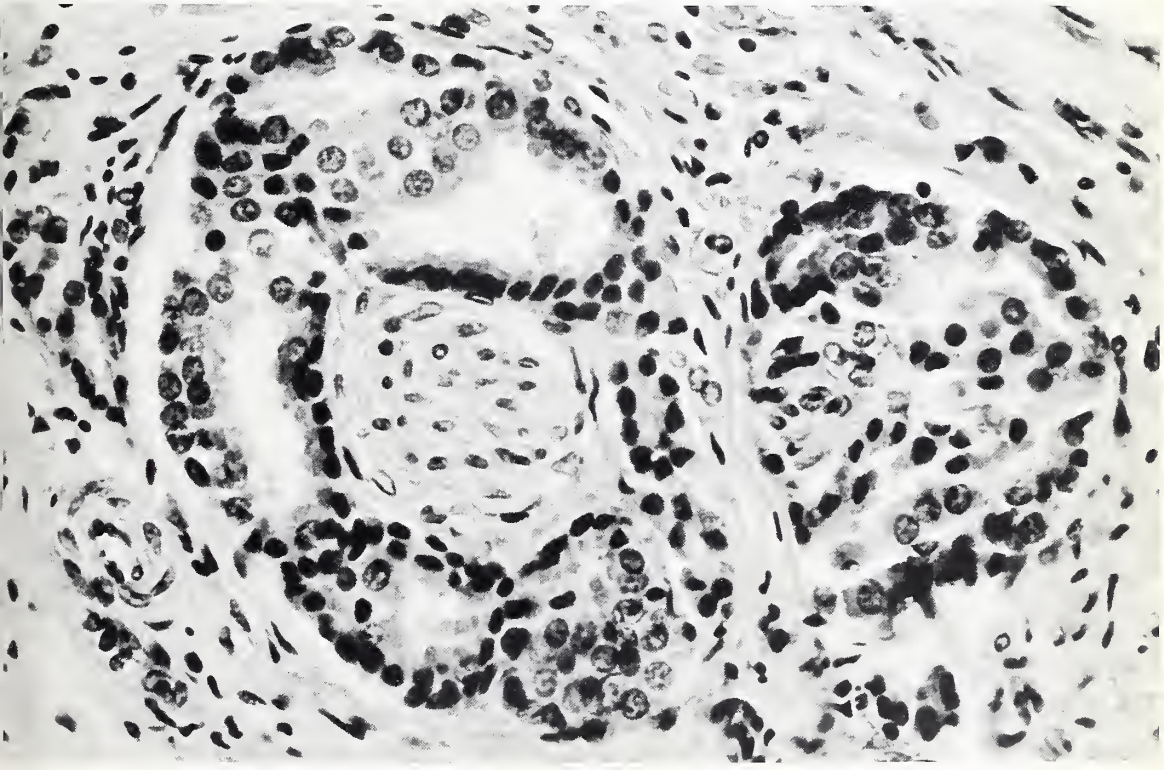

Fig. 13

Figure 14. Recent infarct of prostate. The well circumscribed, slightly discolored infarct bulges on cut surface. Small foci of hemorrhage are visible. (Courtesy of Dr. L. V. Ackerman, Washington University School of Medicine.) A. F. I. P. Acc. No. 218716–27.

Figure 15. Edge of prostatic infarct. The characteristic, but sometimes misleading, prostatic epithelium which has undergone squamous metaplasia lies in the hemorrhagic infarcted stroma. × 75. A. F. I. P. Acc. No. 218716–7.

Figure 16. High power view of metaplastic epithelium in prostatic infarct shown in figure 15. This epithelium appears to be truly epidermoid. Keratin and intercellular bridges may be present. Possible mistake of this relatively common lesion for the almost nonexistent epidermoid carcinoma of the prostate should caution against the latter diagnosis, especially in large nodular glands, which are predisposed to infarcts. × 240. A. F. I. P. Acc. No. 218716–8.

Fig. 14

Fig. 15

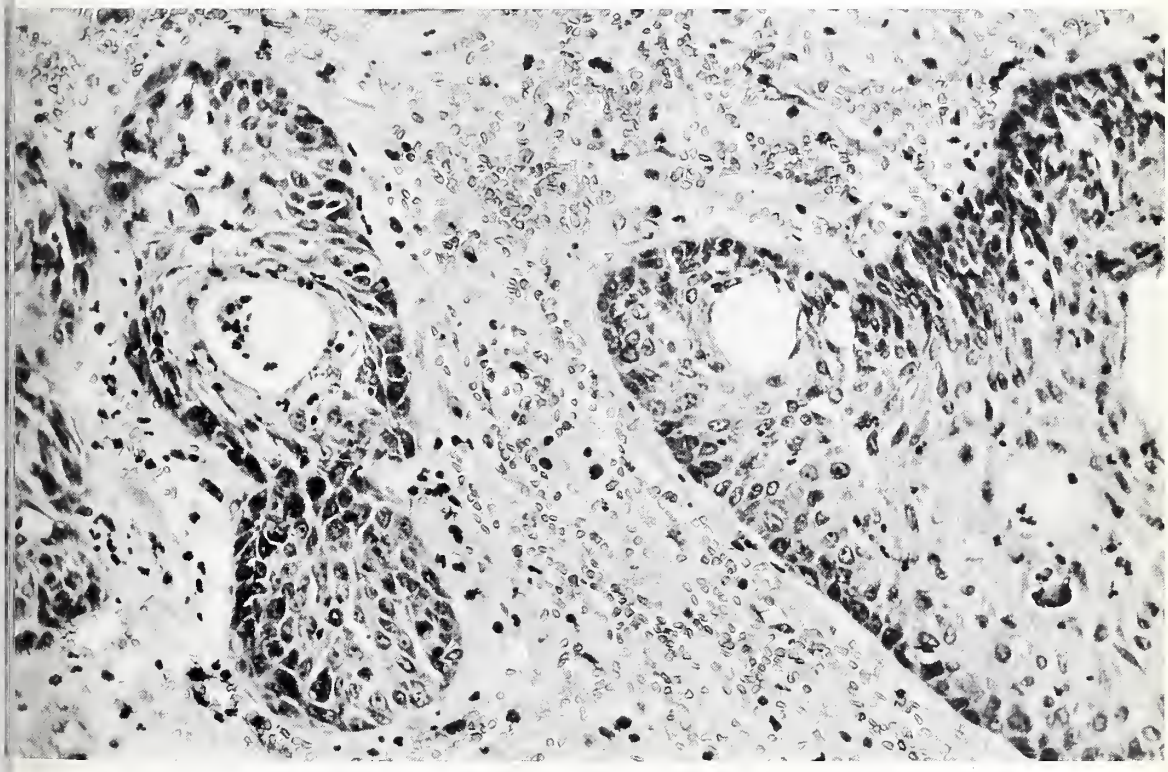

Fig. 16

Figure 17. Estrogen-induced squamous metaplasia of prostatic epithelium. The characteristic keratinized, ballooned cells are frequently found in cases of estrogen administration, or in hepatic cirrhosis, with retention of the estrogens normally present in the male. (Courtesy of Dr. L. V. Ackerman, Washington University School of Medicine.) A. F. I. P. Acc. No. 218716–28.

Figure 18. High power view of adenocarcinoma of prostate to illustrate nuclear and cytoplasmic detail in tumor before estrogen therapy. Note vesicular nuclei, prominent nucleoli, and slightly reticulated cytoplasm. (From Wattenberg, C. A. Bone changes and variations in skeletal metastases due to diethylstilbestrol and orchiectomy during treatment of cancer of the prostate. J. Urol., 58: 378–383, 1947.) A. F. I. P. Acc. No. 218716–29.

Figure 19. Same tumor as in figure 18 after estrogen therapy. Note shrunken structureless nuclei and grossly vacuolated cytoplasm with apparent coalescence of the cells. This change is characteristic of estrogen therapy, but is by no means constant. (Courtesy of Dr. C. A. Wattenberg, St. Louis, Mo.) A. F. I. P. Acc. No. 218716–30.

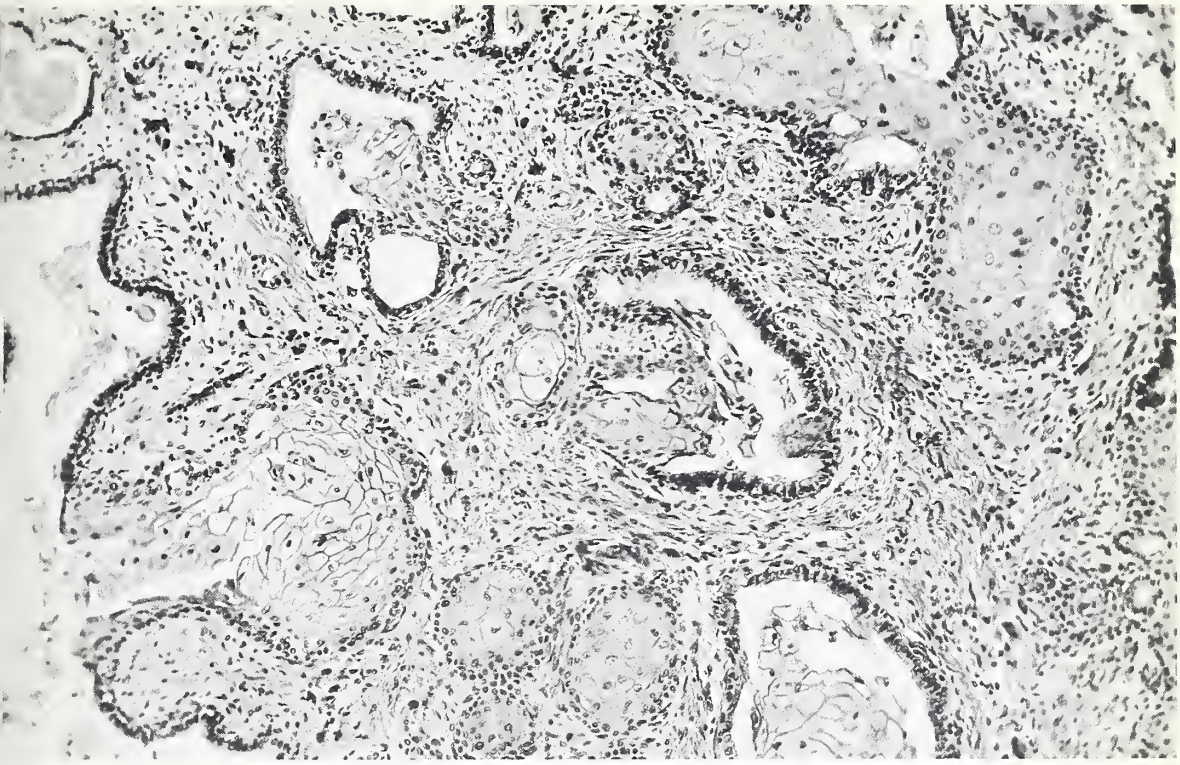

Fig. 17

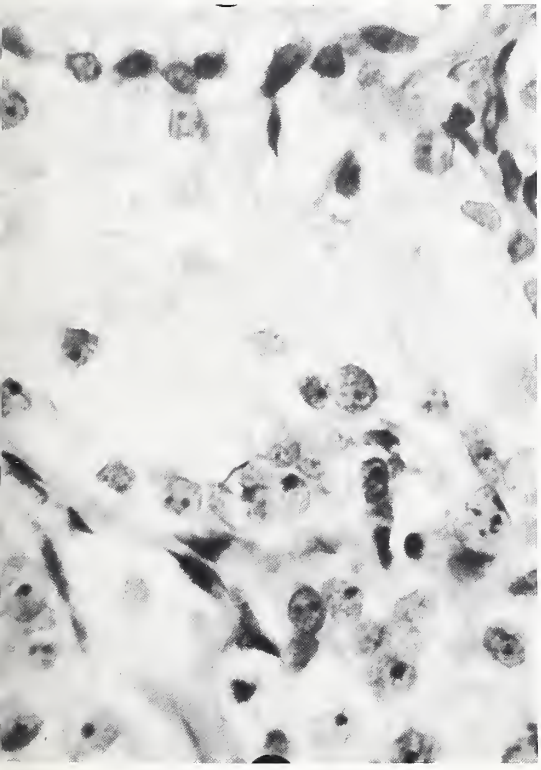

Fig. 18

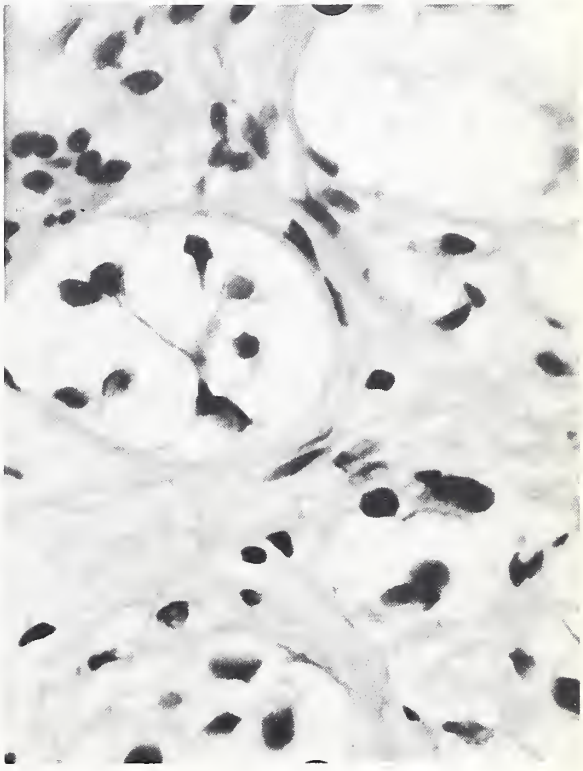

Fig. 19

thickening and occasionally in actual squamous metaplasia. The breasts show typical changes of gynecomastia: proliferation and edema of connective tissue, elongation and budding of ducts, and hyperplasia of the ductal epithelium. A few breast carcinomas have been reported following prolonged estrogen therapy for prostatic carcinoma (Ackerman).

The testes show an inconstant arrest of spermatogenesis and thickening of tubular basement membrane following prolonged estrogen administration.

METASTASES. The frequency of metastases in a series of prostatic carcinomas will, of course, vary widely with the nature of the series of tumors studied—i.e., clinically manifest tumors, autopsies of clinically manifest tumors, or autopsies including both clinically manifest and latent tumors. Of clinically manifest cases, about half develop metastases within a year of onset of symptoms and about 80 percent have metastases at time of death.

Lymph nodes, the most frequent sites of metastases, are involved in 77 percent of fatal cases (Muir). The iliac, periaortic, hypogastric, and sacral nodes are most frequently involved. Later spread may involve the tracheobronchial and supraclavicular nodes.

Osseous metastases are reported in as high as 70 percent of clinically manifest cases (Willis). The pelvis and sacrum are said to be involved in about 85 percent of cases with osseous metastases, the lumbar spine in 59 percent, femora in 35 percent, dorsal spine in 23 percent, and ribs in 22 percent (Graves and Militzer). Osseous metastases characteristically stimulate local bone formation. The increased opacity of metastatic lesions observed radiologically is frequently typical enough to allow diagnosis of the primary condition (figs. 20–22).

Visceral metastases are found in about 40 percent of fatal cases (Willis). They are a late development and occur most frequently in the lungs, liver, and pleura.

There is considerable disagreement concerning the mode of spread and distribution of osseous metastases in prostatic carcinoma. Most observers have found that the bones closest to the prostate—pelvis and lumbar spine—are by far the most frequent sites of metastases. Two explanations for this distribution of metastases have been offered: (1) tumor invasion and extension along perineural lymphatics leading to these bones (Warren, Harris, and Graves); and (2) tumor extension along and embolization of the vertebral venous plexus (Batson).

Willis, however, on the basis of careful necropsy study, disputes this concept of metastases. He claims that prostatic tumor cells are disseminated by systemic circulation, as are the cells of other tumors, and that the distribution of osseous metastases in prostatic carcinoma is the same as that found with other tumors. In support of this idea, he states that minute examination of the lungs will reveal small metastases in almost all necropsies showing bone in-

Figure 20. Typical pelvic roentgenogram in metastatic carcinoma of the prostate. Note densities mottling almost all bones, which indicate osteoblastic metastases. A few radon seeds are visible over the left mid-sacrum. (Courtesy of Dr. W. Seaman, Washington University School of Medicine.) A. F. I. P. Acc. No. 218716–31.

Figure 21. Osteoblastic metastasis of prostatic carcinoma. A semicircular area of increased bone formation and marrow fibrosis is visible. Such lesions are responsible for the areas of radiopacity on the roentgenogram. × 12. (From Friedman, N. B., and Ash, J. E. Atlas of Genitourinary Pathology. Washington, D. C.: American Registry of Pathology, 1946.) A. F. I. P. Acc. No. 111662.

Figure 22. High power view of osteoblastic metastasis of prostatic carcinoma. Osteoblasts are numerous, while osteoclasts are almost nonexistent. Tumor fills all the interosseous spaces. × 137. A. F. I. P. Acc. No. 218716–15.

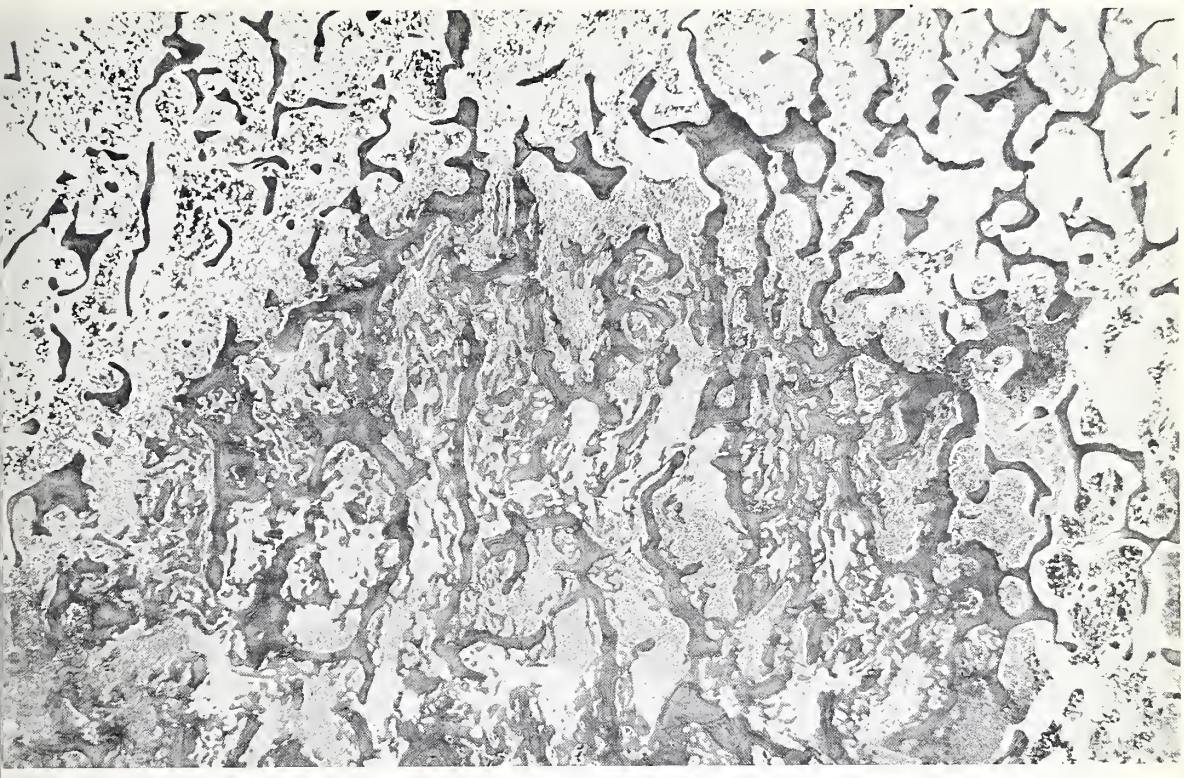

Fig. 21

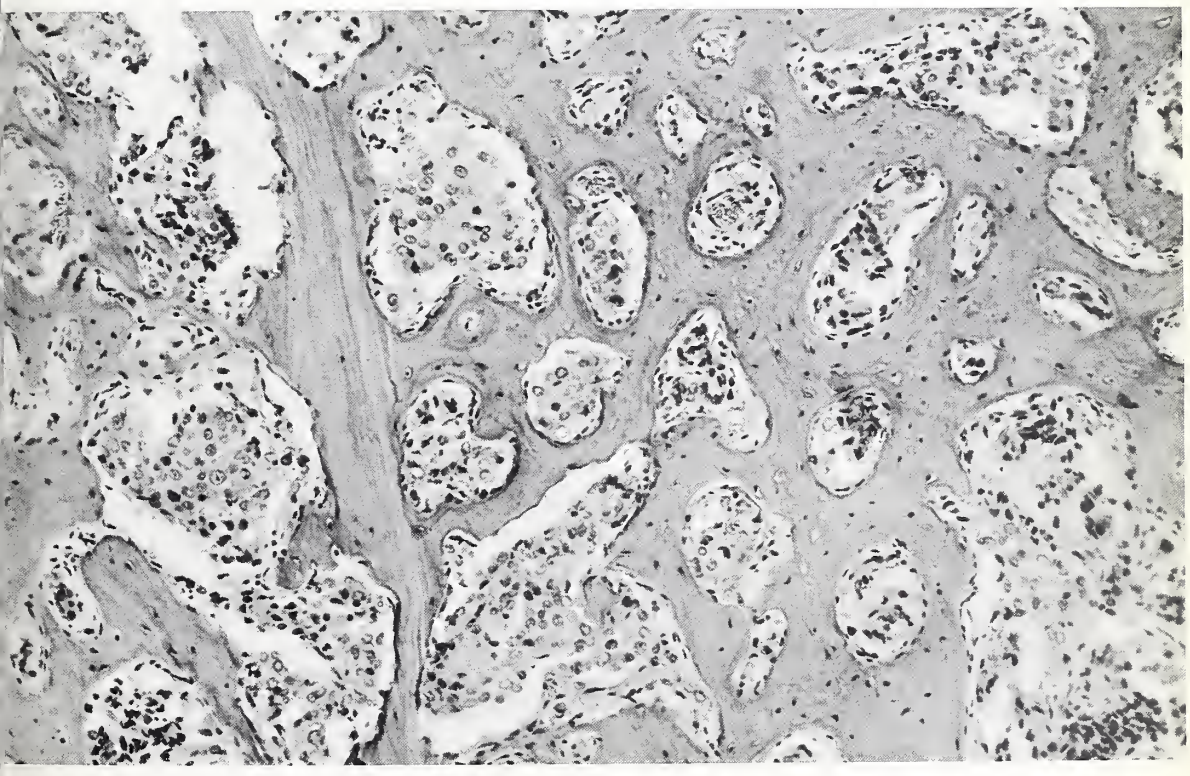

Fig. 22

volvement. The apparent concentration of metastases in bones close to the prostate is merely a result of focusing attention, especially roentgenologic examination, on that region.

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Epidermoid Carcinoma

SYNONYMS AND RELATED TERMS: Squamous cell carcinoma.

Several large series of prostatic tumors give an incidence of epidermoid carcinoma of from two to four percent (Kahler). However, in a review of nearly 500 carcinomas of the prostate in the files of the Armed Forces Institute of Pathology, we have found only one epidermoid carcinoma. This tumor was of low grade malignancy with many well keratinized pearls and little anaplasia (figs. 23, 24). It appeared to arise from the urethral mucosa and invaded the prostate locally. Kahler classified his epidermoid carcinomas as moderately malignant.

It seems most probable that this unusual tumor type is derived from the transitional epithelium of the prostatic urethra and utricle. Nothing is known about the etiologic role of urethritis and squamous metaplasia of urethral epithelium.

Special care should be used in making a diagnosis of epidermoid carcinoma of the prostate both because of its great rarity and because the squa-

Figure 23.* Low grade epidermoid carcinoma involving prostate and appearing to arise in epithelium of prostatic urethra. Invasion, while definite, is limited. × 90. A. F. I. P. Acc. No. 88849–3.

Figure 24.* High power view of tumor seen in figure 23 to show undoubted epidermoid character of tumor cells. Keratin pearls are conspicuous. × 185. A. F. I. P. Acc. No. 88849–4.

*From the Armed Forces Institute of Pathology.

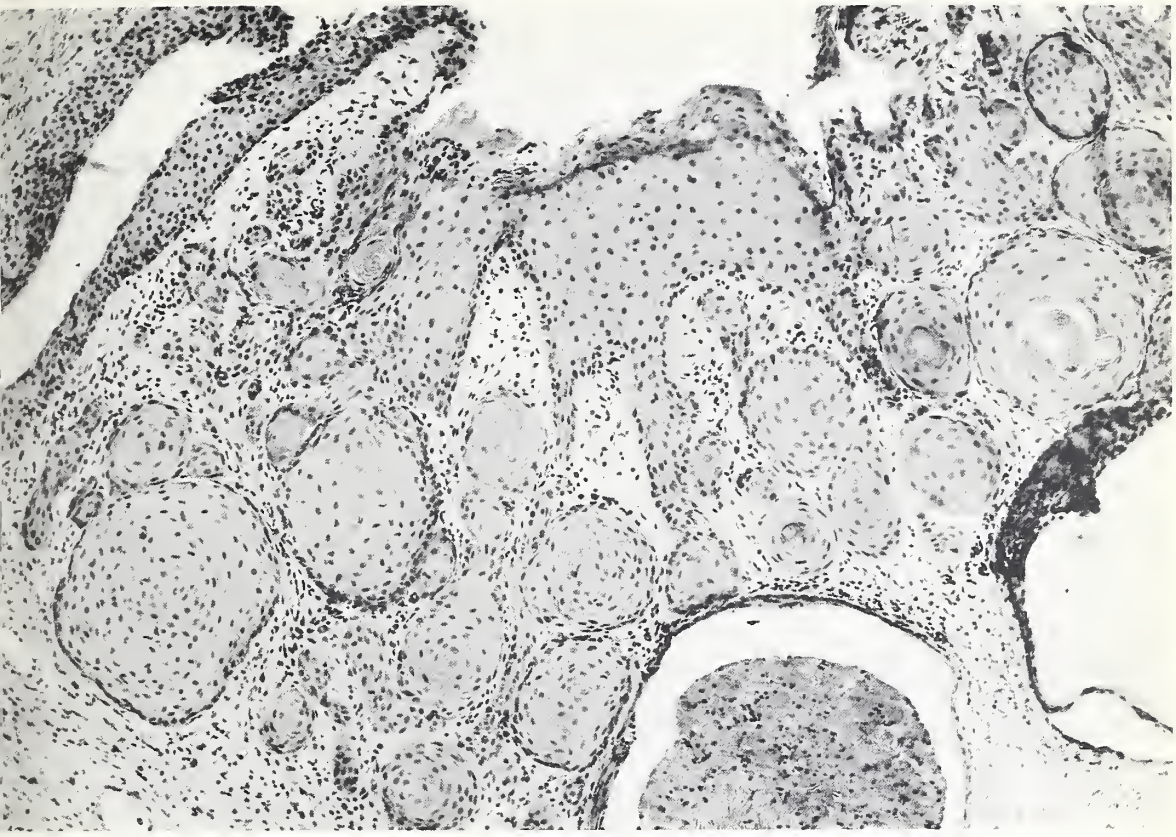

Fig. 23

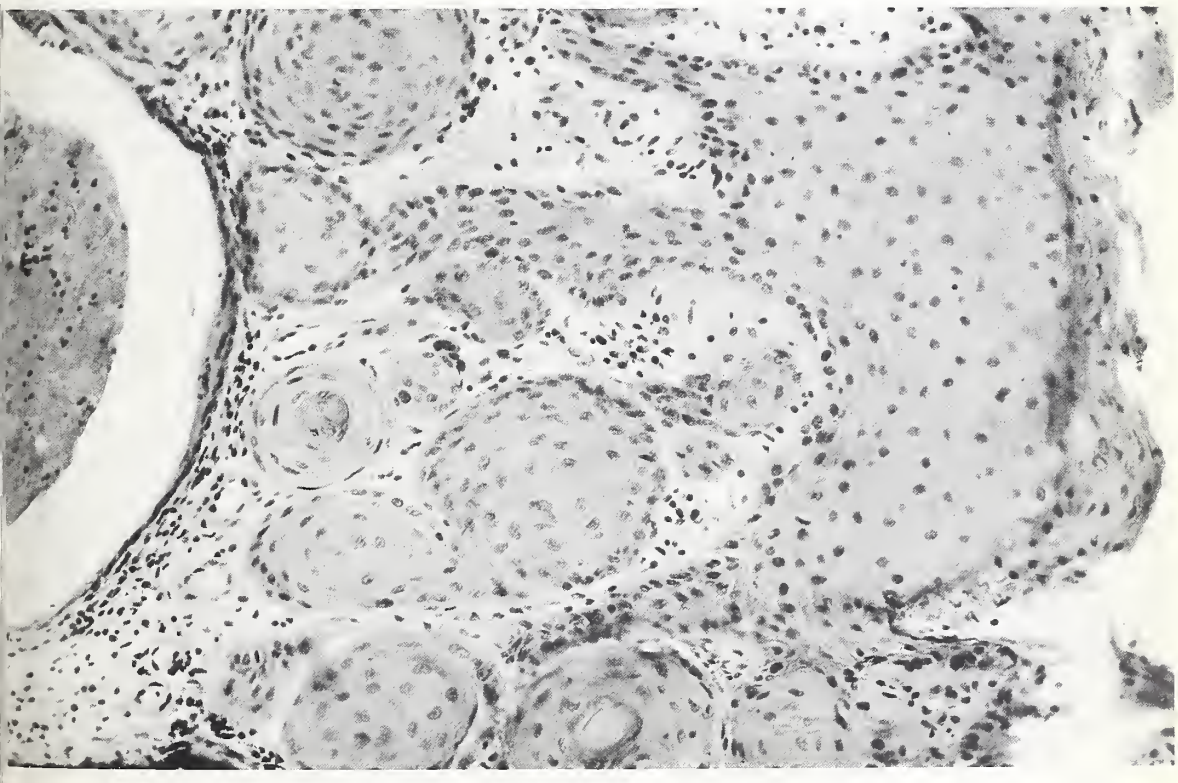

Fig. 24

mous metaplasia of prostatic epithelium found adjacent to infarcts or following estrogen therapy may resemble carcinoma (figs. 15–17).

Reference

Kahler, J. E. Carcinoma of the prostate gland: A pathologic study. J. Urol., 41: 557–574, 1939.

Sarcoma of the Prostate and Neck of the Vesicle

SYNONYMS AND RELATED TERMS: See Fascicle 5, "Tumors of the Soft Tissues."

DEFINITION. Malignant tumors arising from connective tissue elements of the prostate and from tissues of the neck of the vesicle (i. e., fibrous tissue, smooth muscle, striated muscle, lymphoid tissue, and vascular endothelium).

NATURAL HISTORY. The exact point of origin of sarcoma arising in the region of the prostate and the vesical neck can rarely, if ever, be determined. It is, therefore, more proper to consider prostatic and other tissues in the region of the vesical neck together as the source of sarcomas which usually involve the prostate, neck of the vesicle, floor of the bladder, and adjacent structures.

INCIDENCE. Sarcoma of the prostate and of the neck of the vesicle is rare, making up less than 0.1 percent of all fatal prostatic tumors (Sterling and Ash). There are approximately 200 reports of these sarcomas in the literature, many of which may not be sarcomas at all but rather atypical carcinomas.

As with sarcomas elsewhere in the body, sarcoma of the prostate and of the vesical neck is most common in the early decades. Approximately 30 percent occur in the first decade and between 60 and 70 percent are found in the first four decades. The remaining 30 to 40 percent are uniformly distributed throughout the fifth to eighth decades (Melicow, Pelton, and Fish).

COURSE. The sarcomas of infants and children have a much more rapid course and metastasize more widely than those of adults. The average duration from onset of symptoms to death in children under 10 years is about three months, while in adults the average is about one year (Katzen, Cohen, and Steiner).

Death most commonly results from local invasion and urinary obstruction. Local extension and/or regional node involvement or both are found in about 75 percent of patients (Sterling and Ash). Distant metastases occur in about 40 percent of patients with most frequent sites in bones and lungs.

CLINICAL DIAGNOSIS. In young patients diagnosis is not difficult. Painless urinary obstruction with or without bleeding and frequent rectal obstruction are the presenting complaints. A large, smooth, soft to resilient homogeneous mass can be palpated on rectal examination. Occasionally the tumor is large enough to distend the perineum.

In patients over 40 years, the smooth, symmetrical, relatively soft charac-

ter of the tumor differentiates it from the hard, irregular, fixed carcinoma of the prostate. The differentiation from nodular hyperplasia may at times rest on pathologic examination, especially if the tumor is small.

GROSS. These sarcomas vary greatly in size. They attain their largest dimensions in children, where they may fill the entire pelvis. They usually surround the vesical neck with the bulk of the tumor posterior to the urethra, frequently displacing the posterior urethra and floor of the bladder anteriorly and superiorly and so thoroughly distorting the urethra that passage of a sound or catheter is impossible. They are usually roughly ovoid with a relatively smooth surface. In 75 percent of patients there is local invasion, most frequently involving urethra, ureters, seminal vesicles, bladder, and regional nodes.

The consistency varies from a soft, semifluctuant to a resilient character. The firmer tumors are found more frequently in the older patients. In the large, rapidly growing tumors of children, zones of degeneration and necrosis are not uncommon. These necrotic zones are usually hemorrhagic, contrasting with the gray-tan or brown color of the viable tumor.

MICROSCOPIC. Many of the sarcomas of the prostate and of the vesical neck reported in the early literature are impossible to classify histologically. As has already been mentioned, there are no doubt many, especially the so-called "round cell sarcomas," that are actually carcinomas. Many of the cases have been diagnosed according to cell shape—i. e., round cell or spindle cell sarcomas—and, therefore, cannot be satisfactorily classified. It is possible to say only that fibrosarcoma, rhabdomyosarcoma, and leiomyosarcoma are the most frequent histologic types and that lymphosarcoma, myxosarcoma, angiosarcoma, and chondrosarcoma occur less frequently (figs. 25-28).

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Tumor-like Lesions of the Prostate

Nodular hyperplasia of the prostate may at times simulate a true tumor. This lesion, which is found in over 30 percent of men in the fifth and sixth decades and in approximately 70 percent in the seventh, eighth, and ninth decades, consists of a hyperplasia of either stromal or glandular elements or both. The cause of nodular hyperplasia of the prostate has not been determined, although many explanations of its origin have been put forward. The

Figure 25.* Leiomyosarcoma of prostate. Tumor is very cellular, but shows the characteristic interlacing cell bundles, giving a whorled or herringbone appearance. The few remaining ducts and acini are widely scattered in the tumor. × 90. A. F. I. P. Acc. No. 112968–3.

Figure 26.* High power view of rhabdomyosarcoma of prostate to show the cross striations in the tumor cells. Many of the genitourinary sarcomas have architecture suggesting rhabdomyosarcoma, in which no definite cross striations can be found. Myosarcoma is probably the most satisfactory term for such tumors. × 1360. (From Friedman, N. B., and Ash, J. E. Atlas of Genitourinary Pathology. Washington, D. C.: American Registry of Pathology, 1946.) A. F. I. P. Acc. No. 80123.

Figure 27. Rhabdomyosarcoma of prostate. There are none of the large ballooned giant cells so frequently associated with rhabdomyosarcoma, but the elongated straplike cells in several foci show cross striations. × 515. A. F. I. P. Acc. No. 41204–3.

*From the Armed Forces Institute of Pathology.

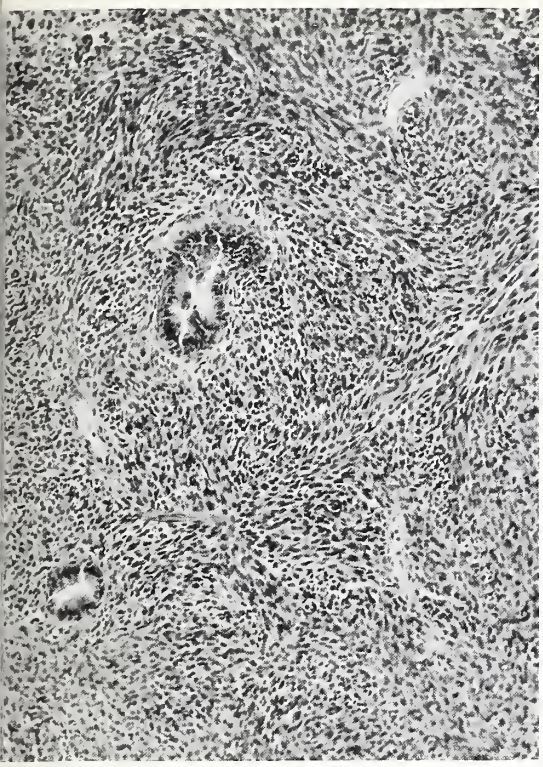

Fig. 25

Fig. 26

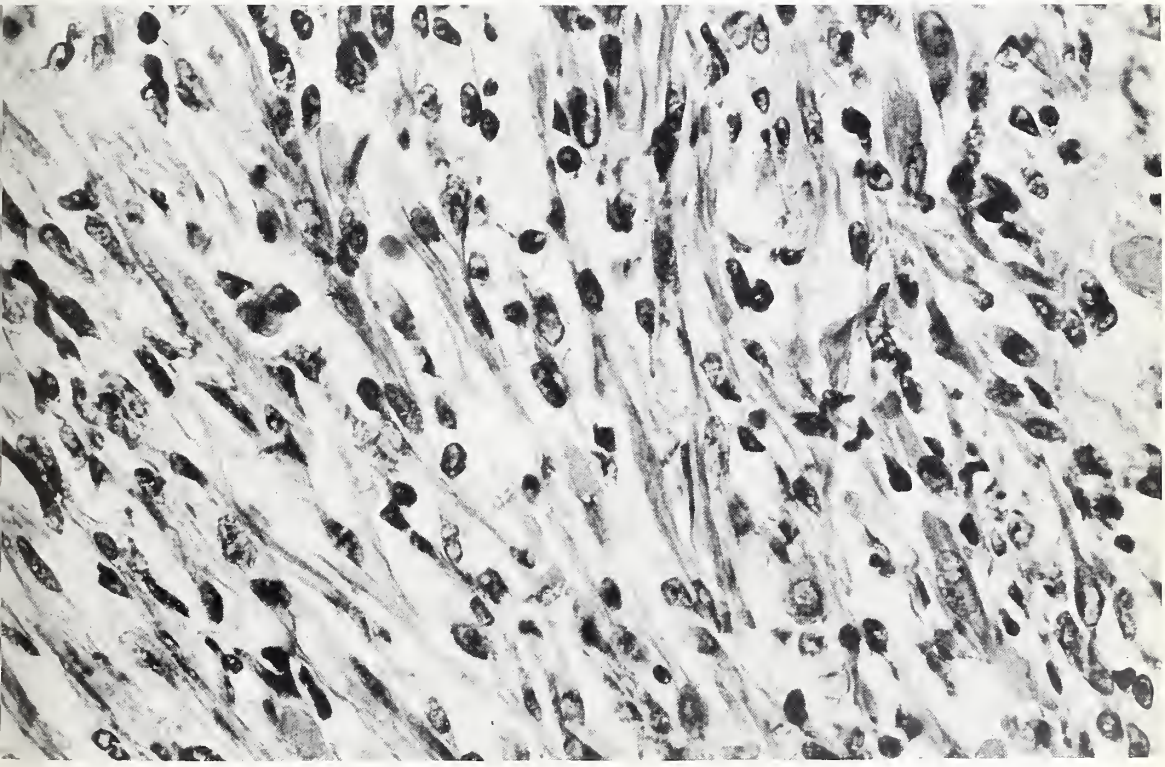

Fig. 27

best evidence available suggests that it results from an imbalance in androgen and estrogen levels in older men (Moore, 1942).

Characteristically, several nodules form in the lateral and middle lobes of the prostate, first in the periurethral stroma and later in the glandular portions. The nodules vary from those composed entirely of fibromuscular tissue to those composed principally of hyperplastic glands, with a majority of nodules a mixture of glands and stroma (figs. 29, 30). The nodules which arise in the periurethral stroma become sharply demarcated, ovoid, dense, white, and fibrillar, and do not bulge from the cut surface (fig. 30). They may be composed primarily of either fibrous or smooth muscle tissue, or they may be a combination of both. They have often been mistaken for leiomyomas. The nodules composed in part of hyperplastic glands are usually spherical, have a yellow-gray granular and sometimes finely cystic cut surface, which bulges slightly (fig. 29). Histologically, the glandular nodules are subdivided into lobules resembling the normal prostate. The stroma may be compressed between the glands, but in all other respects resembles normal stroma. A hyaline basement membrane surrounds all glands. The epithelium may be active, forming papillae and having a variety of cell types, or it may be inactive, composed of small cells resembling those of the prepuberal prostate (Moore, 1942). These nodules have been mistaken for adenomas.

The nodules of nodular hyperplasia are expanding lesions and for that reason superficially resemble true tumors. Microscopically, the pure stromal nodule and the nearly pure glandular nodule also bear some resemblance to neoplasms because of the uniformity of their structure and evidence of active growth. However, several features of these nodules strongly deny neoplasia. They do not tend to become malignant, nor do they have a true capsule, such as is usually found in adenomas. Nodular hyperplasia and carcinoma of the prostate frequently coexist, but they are usually discrete, with carcinoma arising in the posterior lobe and nodular hyperplasia in the lateral and middle lobes. Neither is there any evidence to suggest that sarcomas ever arise from stromal nodules; the majority of sarcomas of the prostate are found in an age group too young to have nodular hyperplasia. Finally, in most hyperplastic prostates there are numerous nodules with structure varying from the pure stromal type to the glandular type, with a majority having intermediate mixtures of the two. This blending of types in the same prostate strongly suggests hyperplasia rather than neoplasia, which is usually derived from a single cell type.

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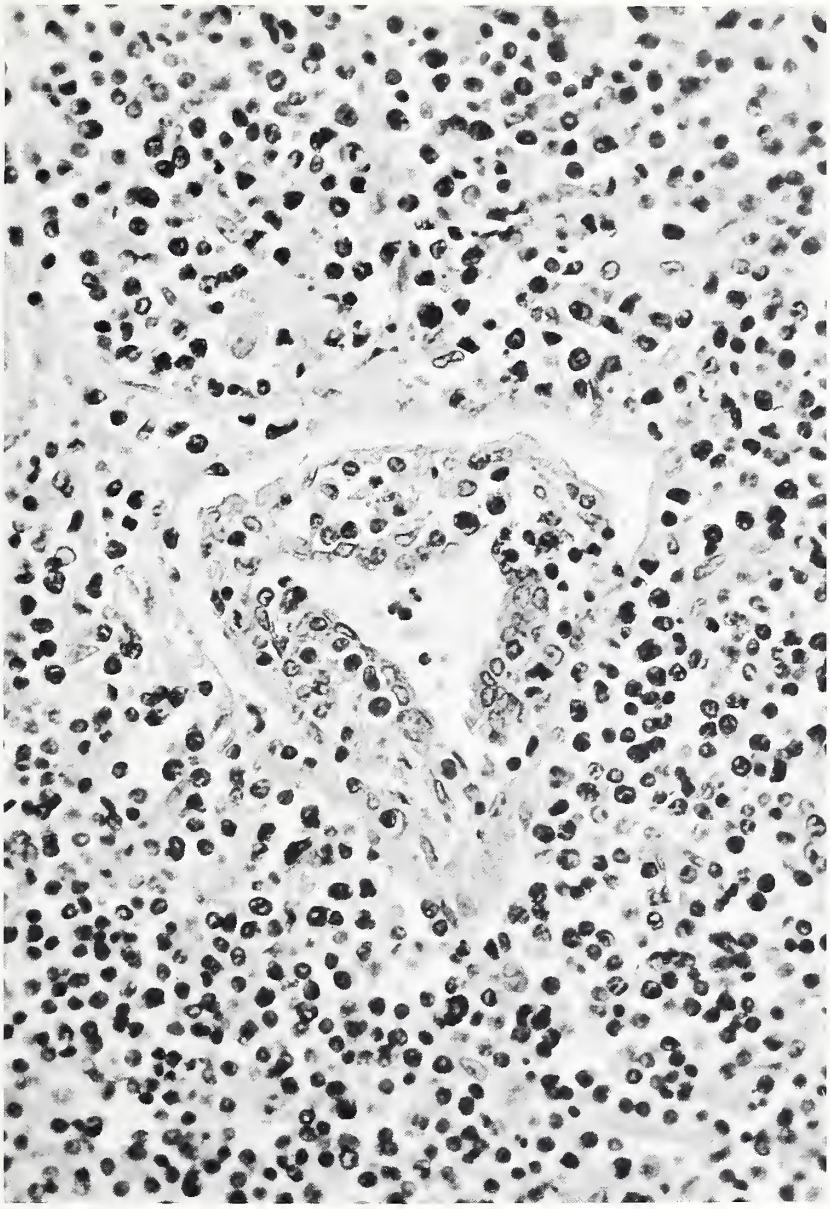

Figure 28. Lymphosarcoma of prostate. A uniform infiltration of large lymphocytes replaces the stroma and also involves the acinus in the center of the photomicrograph. × 355. (Contributed to the Armed Forces Institute of Pathology by Dr. N. P. Rathbun and Dr. J. A. de Veer, Brooklyn, N. Y.) A. F. I. P. Acc. No. 59084–3.

Figure 29. Nodular hyperplasia of prostate, glandular type. In the right lateral lobe is a large, circumscribed, hyperplastic, glandular nodule with honeycombed cystic structure. Note compression of urethra. A. F. I. P. Acc. No. 218716–32.

Figure 30. Nodular hyperplasia of prostate, stromal type. In middle lobe just posterior to the urethra are two white, ovoid, hyperplastic stromal nodules. These characteristically arise near the urethra. A. F. I. P. Acc. No. 218716–33.

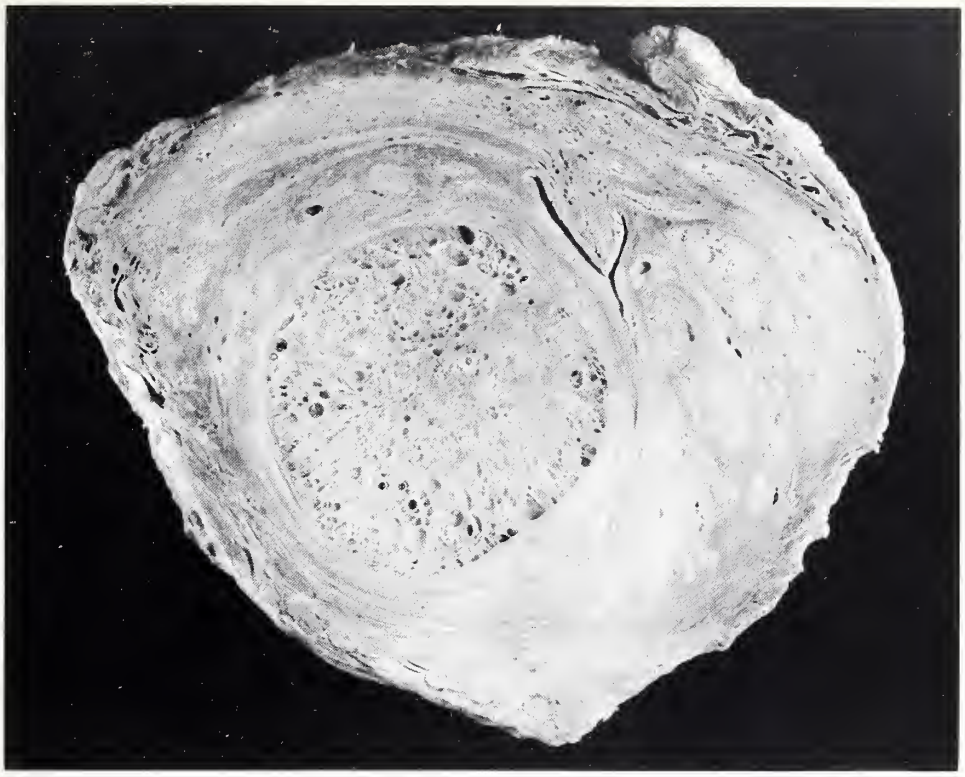

Fig. 29

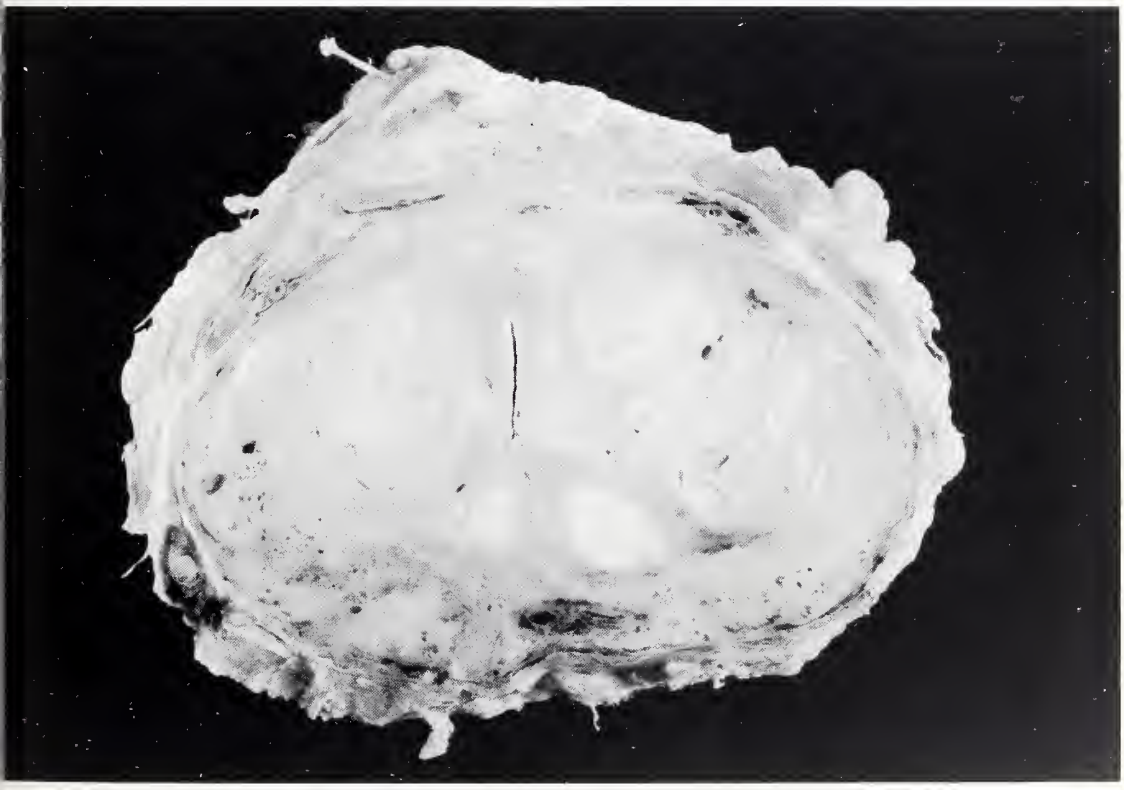

Fig. 30

TUMORS OF THE TESTIS

Introduction

EMBRYOLOGY. The undifferentiated gonads arise on the ventral surface of the mesonephros during the fifth and sixth embryonic week. The site of origin of the primordial sex cells, which are already conspicuous in the gonad at this stage, is of theoretical importance in connection with the genesis of extragonadal teratomas. Some evidence indicates that these cells arise in the entoderm of the yolk sac and migrate to the gonad, while other observations indicate a differentiation in situ from the mesothelium covering the gonad, the germinal epithelium. If the germ cells do arise in the yolk sac and migrate to the gonad, then incomplete or abnormal migration of sex cells could possibly account for extragonadal teratomas. If, on the other hand, the germ cells arise within the gonad, then extragonadal teratomas would be more likely to have a nongerminal origin, perhaps arising from abnormalities in development of the primitive embryonic layers.

Early in the development of the undifferentiated gonad, the covering germinal epithelium with its primordial sex cells forms cordlike extensions into the mesenchyme. In the male, these germinal cords become increasingly distinct and eventually form the seminiferous tubules. In the female, the cords break up, partially into cell clusters, which later become primordial follicles; other remnants of the germinal cords may persist as rudimentary rests in the medulla of the ovary. These rests are thought to give rise to the arrhenoblastomas.

The seminiferous tubules of the 3-month to 5-month male embryo are composed of solid cords of potential germ cells, some of which enlarge at this stage, appear to differentiate precociously, and then degenerate. By the fourth month, the connective tissue immediately beneath the germinal epithelium forms a definite capsule, the tunica albuginea, and the connective tissue between the cords of the testis gives rise to conspicuous masses of interstitial cells. In the hilum, the cords of the testis form an anastomosing network of slender ducts, the rete testis. The rete connects the cords of the testis with the sexual duct system formed from remnants of the mesonephric structures. Several mesonephric tubules and the adjoining portion of the mesonephric duct make up the efferent ductules and ductus epididymidis, while the vas deferens, seminal vesicles, and ejaculatory ducts are all derived from the rest of the mesonephric duct.

ANATOMY. The adult testis is surrounded by the tunica albuginea, a fibrous capsule. At the hilus, fibrous tissue projects from the capsule into the testis, forming the mediastinum; from the mediastinum it extends radially to the capsule as thin septa, dividing the testis into about 250 conical compart-

ments. Each compartment contains one to three convoluted seminiferous tubules. The tubules contain cells of the spermatogenic series (spermatogonia, spermatocytes, spermatids, and sperm) and the supporting Sertoli cells. In the stroma between the tubules, in the rete, in the tunica albuginea, and along the vessels and nerves of the spermatic cord are scattered compact clumps of interstitial cells.

In the progression from the fetal state to the adult there is a gradual maturation of the seminiferous tubules during the prepuberal period. Between the twelfth and sixteenth years spermatogenesis is established, but several years more pass before full gametogenic activity is attained.

Senile changes in the testis, consisting of a decrease in the number of all spermatogenic elements, is extremely variable in time of onset. With a decrease in number of spermatogenic cells, there is an apparent increase in Sertoli cells.

The number of interstitial or Leydig cells of the testis varies greatly in different periods of life and also from individual to individual. The interstitial cells are numerous in late fetal life, presumably as a result of the presence of maternal gonadotropins. After birth the cells regress and remain inconspicuous until puberty, when they again increase in number, reaching a maximum between 10 and 19 years and then gradually diminishing throughout adult life.

Numerous references have been made to the inverse relationship between interstitial cells and testicular tubules. Such a relationship cannot be supported by our observations. Testes with atrophic tubules—whether from radiation, ectopy, or trauma—may have a diminished, normal, or increased number of interstitial cells. With tubular atrophy, however, there is a condensation of the parenchyma; and the resultant relative increase of interstitial cells may give the false impression of an absolute increase.

The internal spermatic arteries, which supply the testis, originate from the abdominal aorta at, or just below, the level of the renal arteries. The right spermatic vein joins the inferior vena cava below the renal veins, and the left spermatic vein joins the left renal vein. The lymphatics of the testis partially follow the supplying blood vessels and drain into the upper lumbar periaortic nodes and nodes around the left renal vein; they also communicate with the external and common iliac nodes and the lower lumbar periaortic nodes. Any or all of these nodes may be involved in metastatic spread of testicular tumors.

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Classification

Testicular tumors can be divided into two general categories: the **germinal tumors,** constituting 96.5 percent of testicular tumors, which arise from cells in the sex or germ series; and the **nongerminal tumors,** constituting 3.5 percent, which arise from the nongerminal elements of the testis.

GERMINAL TUMORS. Numerous classifications for testicular germinal tumors have been proposed without, until recently, any general agreement. Within the past few years, several large series of testicular tumors have been studied by various investigators, all of whom are in basic agreement regarding classification. Four main histologic patterns in germinal tumors (with minor variations in nomenclature) are recognized by these workers: seminoma, embryonal carcinoma, teratoma, and choriocarcinoma. On the basis of histologic study we have postulated an interrelationship of these patterns, as illustrated in figure 31.

Seminomas (figs. 34–43) are composed of uniform large cells with clear cytoplasm; they may or may not have lymphoid stroma. Although of germinal origin, they are not intimately related to the other types of germinal tumors. While seminomas are often found in the same testis with other types, they are usually distinct and separate. They frequently appear as satellite nodules, suggesting an origin secondary to the presence of a pre-existing tumor.

Embryonal carcinomas, choriocarcinomas, and **teratomas** are closely related tumors, as indicated in figure 31. On the basis of morphologic observation, it is most likely that the earliest form in this group of tumors is **embryonal carcinoma,** composed of nearly totipotential, undifferentiated cells (figs. 48–59). This tumor presumably arises from a germ cell and may under certain conditions undergo either trophoblastic or somatic differentiation or both. Whether this differentiation must pass through stages resembling those in early embryos, i. e., whether the tumor is of true parthenogenetic origin, is not settled. In numerous instances, structures bearing resemblance to early embryos can be found associated with partial differentiation. In other tumors, however, somatic or trophoblastic differentiation appears to take place within a mass of undifferentiated cells with no transitional embryoid stages. Early trophoblastic differentiation of the multipotential embryonal carcinoma cells results in a tumor composed predominantly of cytotrophoblastic elements that is included as a variety of embryonal carcinoma. The category **choriocarcinoma** is reserved for those tumors showing both cytotrophoblast and syn-

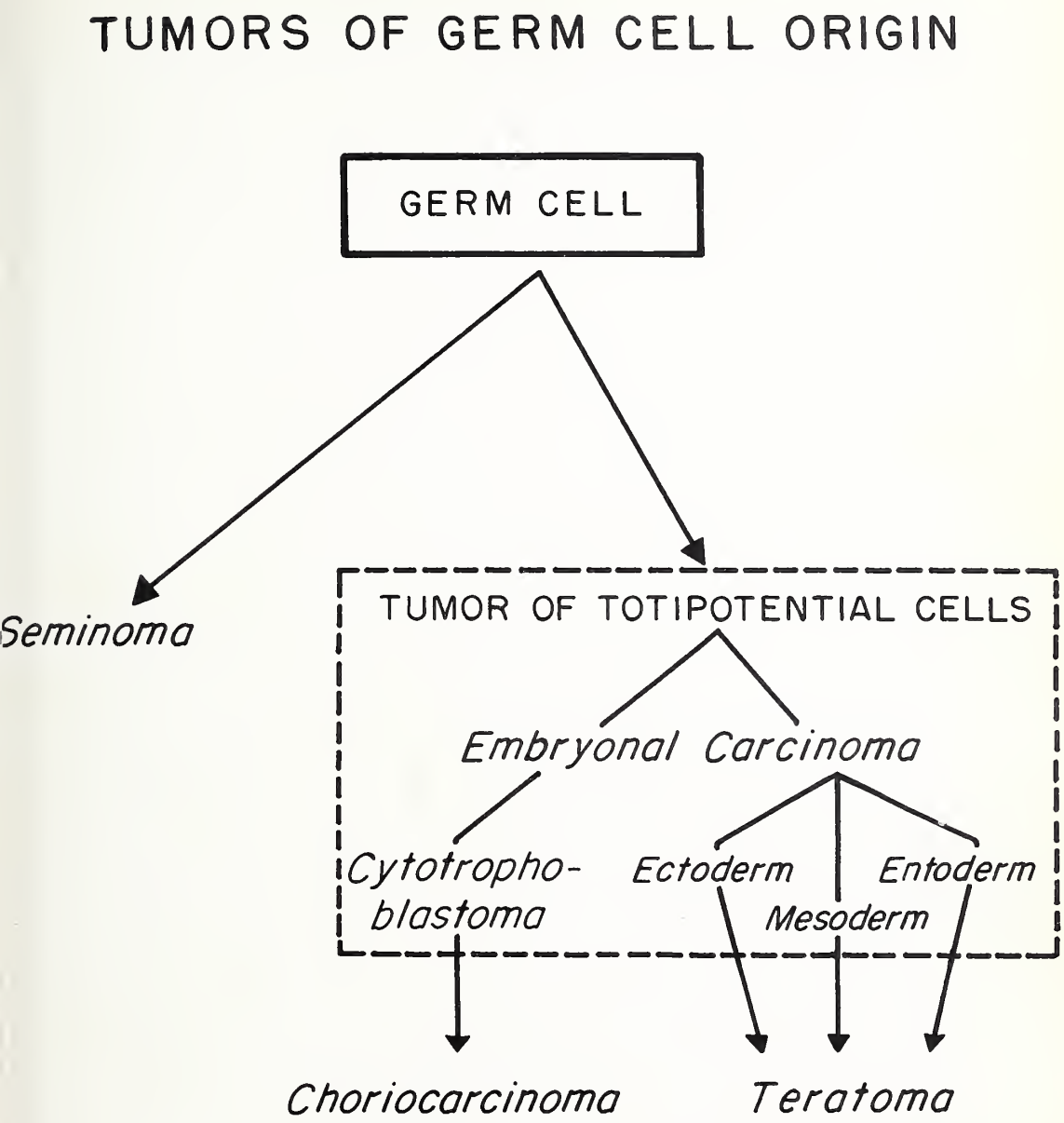

Figure 31. Diagram postulating interrelationship of testicular tumors derived from germ cells.
A. F. I. P. Acc. No. 218716–35.

cytial trophoblast in villus-like arrangement (figs. 69–71). Early somatic differentiation results in embryonic epithelial structures and stroma of unidentifiable types. Tumors manifesting these early stages of somatic differentiation are also considered a variety of embryonal carcinoma. The inclusion of morphologically different although histogenetically related tumors within the embryonal carcinoma group is desirable for practical purposes since all these early, slightly differentiated tumors have identical prognoses. Only when the differentiation results in the formation of recognizable fetal or adult tissues is the term **teratoma** applied (figs. 61–68). The multipotentiality of this trio of tumors—embryonal carcinoma, choriocarcinoma, and teratoma—strongly suggests origin from a totipotential cell of the germinal series.

The problem of diagnosis of germinal tumors is not the recognition of these four characteristic histologic patterns but rather the proper classification of the various pure and mixed varieties. The germinal tumors may be composed of one or any combination of these four patterns, resulting in 15 possible varieties—an all too complicated division. However, two denominators of behavior that are present in these various combinations make possible a more simple classification. First, seminoma as a pure tumor is much less malignant than the other three types but when mixed with other types it has no influence on the course of the more malignant neoplastic process. Second, whenever teratoma coexists with either embryonal carcinoma or choriocarcinoma or both, the extremely malignant character of the latter two varieties is definitely ameliorated.

On the basis of the above observations, we have classified the 15 possible varieties of germinal tumors in five groups, each of which has distinctive clinical behavior:

I. Seminoma, pure
II. Embryonal carcinoma, pure or with seminoma
III. Teratoma, pure or with seminoma
IV. Teratoma with either embryonal carcinoma or choriocarcinoma or both and with or without seminoma
V. Choriocarcinoma, pure or with either seminoma or embryonal carcinoma or both

NONGERMINAL TUMORS. The rare nongerminal tumors, which comprise 3.5 percent of testicular tumors, are extremely varied. They include interstitial cell tumors, androblastomas, fibromas (usually from the tunica), fibrosarcomas, angiomas, neurofibromas, adenomatoid tumors (most often in the epididymis, but occasionally within the testis), and adenocarcinomas of the rete. Of all these tumors, only the interstitial cell tumors, androblastomas, and rete carcinomas are specifically gonadal. The remaining varieties are similar to their counterparts originating elsewhere in the body.

Other benign and malignant connective tissue tumors have been reported

in the testis, but they are probably not true nongerminal testicular tumors. The rhabdomyomas, rhabdomyosarcomas, chondromas, and chondrosarcomas reported in the early literature probably represent one-sided development of teratomas rather than pure primary tumors. The lymphomas reported in the testis are almost always associated with obvious generalized involvement.

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Comparison of Testicular and Ovarian Tumors

Teilum has emphasized the fact that the tumors of testis and ovary are in great part homologous. All of the germinal tumors of the testis have counterparts in the ovary. Seminomas of the testis correspond to dysgerminomas of the ovary, while undifferentiated embryonal carcinomas, teratomas, and choriocarcinomas are found in both testis and ovary. A rare interstitial cell tumor may be seen in the hilus of the ovary. Androblastomas are entirely comparable to the various types of ovarian arrhenoblastomas. However, the incidence of these tumors differs in the two sexes, e. g., adult teratomas (dermoids) are common in the female and relatively rare in the male, while seminomas and embryonal carcinomas are common testicular tumors with rare ovarian counterparts. If the morphogenesis of teratomas in both sexes is, as we propose for the male, from an undifferentiated embryonal carcinoma, it would seem that something in the female environment predisposes to adult somatic differentiation, while the male environment fosters undifferentiated malignant growth.

Considering the above mentioned homologous testicular and ovarian tumors, it appears that the ovary is more versatile in forming tumors than the testis, since no counterparts of ovarian cystadenomas and granulosa-theca cell tumors have been seen in the testis.

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Incidence

The incidence of testicular tumors in the male army population from 1940 to 1947 was 2.88 per 100,000 per year, based on histologically confirmed cases in the files of the Armed Forces Institute of Pathology. This population was made up chiefly of men between the ages of 20 and 30. The estimated incidence in the male civilian population, 18–44 years, based on army figures for

1943 to 1944 would be 3.14 per 100,000 per year, as compared with an army incidence of 2.63 for those years. The difference arises from the increased proportion of civilian men in the fourth decade, where the incidence of testicular tumors is highest

The frequency of testicular tumors in relation to all malignant neoplasms found in army men according to age groups is shown in table I. According to civilian data cited by Gilbert and Hamilton, testicular tumors comprise about 1.5 to 2.0 percent of all malignant tumors of the male and 9.5 percent of the malignant tumors of the male genitourinary tract. U. S. Bureau of Census figures attribute 0.64 percent of all male cancer deaths to testicular tumors.

Table I*

INCIDENCE OF TESTICULAR TUMORS

Percentage of all Cancers found in White Male Army Population in 1944 which Occurred in the Testis

Age in years	Percentage of all cancers found in Army men which occurred in testis	Age in years	Percentage of all cancers found in Army men which occurred in testis
< 20	5.2	35 to 39	6.2
20 to 24	9.9	40 to 44	3.4
25 to 29	13.2	> 45	.6
30 to 34	11.0	All ages**	9.0

*From: Lindsey, D., and Cohart, E. M. Incidence of cancer in American males. Cancer, 3: 945-959, 1950.

**Based on our figures of army population by age.

A study of 990 testicular tumors found in the files of the Armed Forces Institute of Pathology through 1947 showed the following division: 96.5 percent germinal, 3.5 percent nongerminal. The distribution of germinal tumors according to the groups outlined on page 52 was as follows: tumor group I, 38.2 percent of cases; tumor group II, 20.3 percent; tumor group III, 8.6 percent; tumor group IV, 31.6 percent; tumor group V, 1.3 percent.

The incidence of germinal tumors was highest between the ages of 25 and 34 and was progressively less in both younger and older age groups. The tendency for seminoma to occur in older men was not so striking in the army series as in others previously reported.

Only 1.5 percent of the germinal tumors occurred in nonwhites, despite the fact that the nonwhites in the army varied from about 6.0 to 8.5 percent. No explanation of this apparent race difference is at present available.

The tumor incidence was approximately equal for right and left testes; actually 54 percent right and 46 percent left. However, the incidence was greatly increased in undescended testes. Twenty-four of the 990 testicular tumors originated in undescended testes. On the basis of Selective Service

figures of about 0.25 percent of selectees with undescended testes, the chance that a tumor would develop in an undescended testis is slightly more than 11 times that for a scrotal testis. Analysis of testicular tumors reported in the literature shows a frequency of occurrence for tumors in ectopic testes of 48 times that in scrotal testes. The frequency of tumors in abdominal testes in this survey was found to be four times that for inguinal testes. According to these figures, one abdominal testis in 20 might be expected to undergo malignant change and one inguinal testis in 80.

Of the 24 tumors in undescended testes in the army series, 17 were seminomas, indicating a marked predisposition toward this type of tumor in ectopic testes.

The 35 nongerminal tumors in the army study were diagnosed as follows: capsular fibromas, 14; interstitial cell tumors, 12; androblastomas, 4; adrenal or cortical rest tumors, 2; neurilemoma, 1; adenomatoid tumor, 1; sarcoma, 1. These tumors showed no predilection for age group, race, or testicular location.

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GERMINAL TUMORS

The germinal tumors are composed of one or any combination of four distinct histologic patterns: seminoma, embryonal carcinoma, teratoma, and choriocarcinoma. We have grouped the 15 possible histologic combinations of germinal tumors into five classes according to their biologic behavior and postulated morphogenesis (see page 52).

Mortality is the most positive measure of the biologic activity of these tumors. The mortality figures in table II show the different degrees of malignancy of each of the five groups under the more or less uniform conditions of treatment used in these army cases. They emphasize the practical clinical value of this classification.

The following discussion of the clinical and pathologic aspects of each of these tumor groups is based on our study of testicular tumors in the United States Army population from 1940 to 1947. The data from this study, as summarized in table II, show favorable prognostic signs to be no pain, negative urinary gonadotropin, no metastases at first examination, no extension outside testis, no vascular invasion, and no hyperplasia of interstitial cells. Factors of no significance in any type of testicular tumor were size of tumor and duration of symptoms before treatment. Retroperitoneal node dis-

Table II

EVALUATION OF FACTORS INFLUENCING THE MORTALITY RATE OF GERMINAL TUMORS OF THE TESTIS

Based on a follow-up study of 990 cases at the Armed Forces Institute of Pathology
under a contract with the Veterans Administration

GROUP	Tumor group as percent of all tumors in 1934-1944*		PROGNOSTIC FACTORS AND MORTALITY Percent of operable cases dying of tumor within 2 years of operation															
			Over-all mortality. Percent of operable cases dying of tumor, by time from operation		Pain		Urinary gonadotropin pre-operatively		Metastases at first examination		Extension local		Lymphoid stroma		Vascular invasion		Hyperplasia of interstitial cells	
	Army	Total U.S. males**	2 yrs.	5 yrs.	With	Without	Positive	Negative	Yes	No	Outside testes	No extension	Yes	No	Yes	No	Yes	No
I (Pure Seminoma)	34.0	40.6	6.4	10.5	10	4	20	4	32	4	15	6	4	12	15	6	32	5
II (Embryonal carcinoma with or without seminoma)	22.5	29.9	58.7	64.5	68	47	85	50	92	46	82	47	.....	.....	74	36	81	49
III (Teratoma with or without seminoma)	10.2	9.2	26.1	29.2	40	18	.....	.....	93	9	57	15	.....	.....	.....	.....	71	21
IV (Teratoma with embryonal carcinoma and/or chorio-carcinoma and with or without seminoma)	31.1	19.0	47.9	52.2	.....	.....	69	47	84	41	70	43	.....	.....	.....	.....	69	47
V (Choriocarcinoma with or without embryonal carcinoma and/or seminoma)	2.1	1.1	83.3	100	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....

*Comparison of Army incidence with estimated total incidence based on Army 1943-1944 experience only.

**Estimated proportions in U.S. males 18-44 years of age by application of Army age-specific incidence to U.S. male population.

section was of value as an adjunct to roentgen therapy in Groups II, III, and IV, but added nothing to roentgen therapy in the extremely radiosensitive Group I tumors.

The mortality rates for the army series are considerably lower than those for other testicular tumor reports in the literature. Two factors may be responsible for this: first, the frequency of physical examinations in the army, resulting probably in earlier detection; and second, the frequency of roentgen therapy (a factor of special importance in Group I tumors). It should also be noted that mortality figures are based on operable cases only and not on the entire series.

Tumor Group I—Seminoma, Pure

SYNONYMS AND RELATED TERMS: Disgerminoma, dysgerminoma; "embryonal carcinoma with lymphoid stroma"; germinoma; gonocytoma; large cell carcinoma; large cellular medullary carcinoma; "mesenchymoblastoma"; monocellular testicular tumor; seminal carcinoma; spermatoblastoma; spermatocytoma.

DEFINITION. A gonadal tumor of relatively low malignancy and extreme radiosensitivity. It is made up of characteristic large, uniform cells with clear cytoplasm that resemble spermatogonia.

INCIDENCE. Tumor Group I is the most common variety of testicular tumor. About 38 percent of germinal tumors occurring in the military population were seminomas. Based on these figures, seminomas in the total population would be expected to comprise about 41 percent of germinal tumors. The difference is caused by a slightly increased incidence of seminoma in older age groups.

CLINICAL COURSE. The two most common complaints of army patients with Group I tumors were gradual swelling of the testes (75 percent) and pain (43 percent). About one half of these men had symptoms for more than six months before seeking medical aid. At time of first examination, 11 percent had clinically demonstrable metastases.

Positive urinary gonadotropin tests were obtained in 13 percent of the patients tested preoperatively and in about 6 percent tested after removal of the testis. The method for these assays was not constant, and no attempt was made to differentiate between chorionic and pituitary gonadotropin.

Treatment of the army patients included orchiectomy, with or without retroperitoneal node dissection, and postoperative radiation in 93 percent; surgery alone in 4 percent; and palliative roentgen therapy or no treatment in 3 percent. In the 97 percent of cases treated either by surgery and radiation or by surgery alone, 6.4 percent died within two years after operation and 10.5 percent within five years. The mortality rate was highest during the first three years and then dropped so that virtually all tumor deaths observed occurred within five years after operation (table III).

Several clinical features in the patients with Group I tumors proved

Table III

ANNUAL MORTALITY, FIRST FIVE YEARS AFTER OPERATION FOR TESTICULAR TUMORS

Rates represent number of deaths from tumors per 100 survivors at beginning of each year.

Tumor group	Years after operation				
	1st	2nd	3rd	4th	5th
I	3.2	3.3	3.2	1.2	.....
II	40.4	30.7	9.8	2.0	2.7
III	22.1	5.4	2.0	2.2	.....
IV	30.6	24.9	7.5	.9	.....

to be of prognostic significance. Those patients with complaint of pain had a 10 percent 2-year mortality and those with no pain, a 4 percent mortality. Patients with positive urinary gonadotropin tests preoperatively had a 20 percent 2-year mortality and those with negative tests, a 3.6 percent mortality. Patients with metastases demonstrable at first examination had a 32 percent 2-year mortality and those with no metastases a 4.4 percent mortality. There was no evidence that duration of symptoms before treatment or use of retroperitoneal node dissection had any effect on prognosis.

The salvage of a majority of patients with clinically demonstrable metastases was apparently the result of roentgen treatment. These tumors are extremely radiosensitive: 1,000–1,200 r delivered to the tumor is sufficient in most cases. Because of this radiosensitivity, Lewis recommends routine radiation of all regional nodes to the level of the renal pedicles at the time of surgery in order to destroy any metastases. Some success has been reported in using radiation to treat pulmonary metastases.

GROSS. Tumors of Group I, pure seminomas, are among the largest testicular tumors, with a mean volume of 89 cc. The seminoma usually replaces the testis with firm, resilient tumor tissue, expanding it uniformly (figs. 32, 33). The capsule of the testis is smooth or slightly lobulated. Extension of the tumor beyond the capsule, usually into the epididymis or spermatic cord, occurred in 8 percent of army cases. There was no relation between size of tumor on the one hand and extratesticular extension, metastases, or prognosis on the other. However, the presence of extension beyond the testis was associated with a 15 percent 2–year mortality and absence of extension with a 6 percent mortality.

On section the cut surfaces bulge and are for the most part firm, homogeneous, gray-white, and glistening. Geographically outlined regions of

ischemic necrosis are common, and in rare instances small hemorrhagic foci are present (fig. 33).

Distribution of metastases as determined from 36 autopsies was as follows: periaortic and iliac lymph nodes, 71 percent of autopsies; liver, 54 percent; right lung, 38 percent; left lung, 35 percent; left kidney, 37 percent; right kidney, 6 percent; left adrenal, 35 percent; right adrenal, 9 percent; pancreas, 21 percent; peritoneum, 22 percent; and pleura, 17 percent. The greater involvement of the left kidney and adrenal over the right is presumably related to the emptying of lymphatics from the left testis into nodes about the left renal vein as contrasted to the emptying of the lymphatics on the right directly into the periaortic chain.

MICROSCOPIC. Group I tumors are made up of large, round or polyhedral cells with distinct cell borders, clear cytoplasm, and large, centrally placed, deeply chromatic, round nuclei having one or two prominent nucleoli (figs. 34–37). The cells are closely packed and often separated into lobules by a characteristic partitioning stroma. The stroma may be inconspicuous or prominent and varies from lymphoid to granulomatous or scirrhous in nature (figs. 38–40). The foci of ischemic necrosis seen grossly contain shadow or ghost cells that retain the outline of the living cell but have no cellular detail. Such areas of necrosis are characteristic of seminomas.

Intratubular growth was present in 24 percent of Group I tumors (figs. 42, 43). In 14 percent, occasional trophoblastic cells were present that varied from typical syncytial giant cells to narrow, dark, elongated cells resembling early stages of syncytial trophoblastic development (fig. 41).

In all respects, Group I tumors were morphologically identical with the seminomatous regions found in the mixed tumors.

The histologic structure of the metastases associated with 23 Group I tumors was as follows: seminoma in 65 percent of cases, embryonal carcinoma in 26 percent, teratoma in 4 percent, and choriocarcinoma in 9 percent. The most likely origin for the nonseminomatous metastases would seem to be undetected nonseminomatous foci in the primary, since transitions from seminoma to other tumor patterns have not been found.

Two histologic features of these tumors were of prognostic value. Those tumors with definite lymphoid stroma had a 4 percent 2–year mortality and those with no lymphoid stroma a 12 percent. Vascular invasion by tumor was associated with a 15.2 percent 2–year mortality, and absence of vascular invasion with a 5.6 percent.

In all tumor groups hyperplasia of the interstitial cells in the surgically removed testis was correlated with a poor prognosis. In Group I hyperplastic interstitial cells were associated with a 32 percent 2–year mortality and normal interstitial cells with a 5 percent. This hyperplasia of interstitial cells may well reflect the presence of chorionic gonadotropin, which is also

Figure 32.* Seminoma, testis. On section discrete spherical tumor nodules show bulging, homogeneous, white, soft surface. In small tumors such as this one, necrosis of tumor is not common. Testicular parenchyma is seen superiorly and laterally in each cut surface. Tunica albuginea appears intact over surface of tumor. A. F. I. P. Acc. No. 193004.

Figure 33.* Seminoma, testis. Cut surface of tumor which has greatly enlarged the testis and almost completely replaced testicular parenchyma. The soft, bulging, grey-white tumor contains numerous geographically outlined infarcts. Such foci of coagulative necrosis are almost always found in large seminomas. Tunica albuginea does not show gross invasion by tumor. A. F. I. P. Acc. No. 216066.

*From the Armed Forces Institute of Pathology.

Fig. 32

Fig. 33

Figure 34.* Seminoma showing uniform tumor cells and relatively regular fine branching supporting stroma with a few scattered lymphocytes. × 155. A. F. I. P. Acc. No. 141764.

Figure 35.* Seminoma. Note regularity of supporting stroma which divides tumor into lobules. Cytoplasm of these tumor cells takes little or no stain. × 180. A. F. I. P. Acc. No. 183874.

*From the Armed Forces Institute of Pathology.

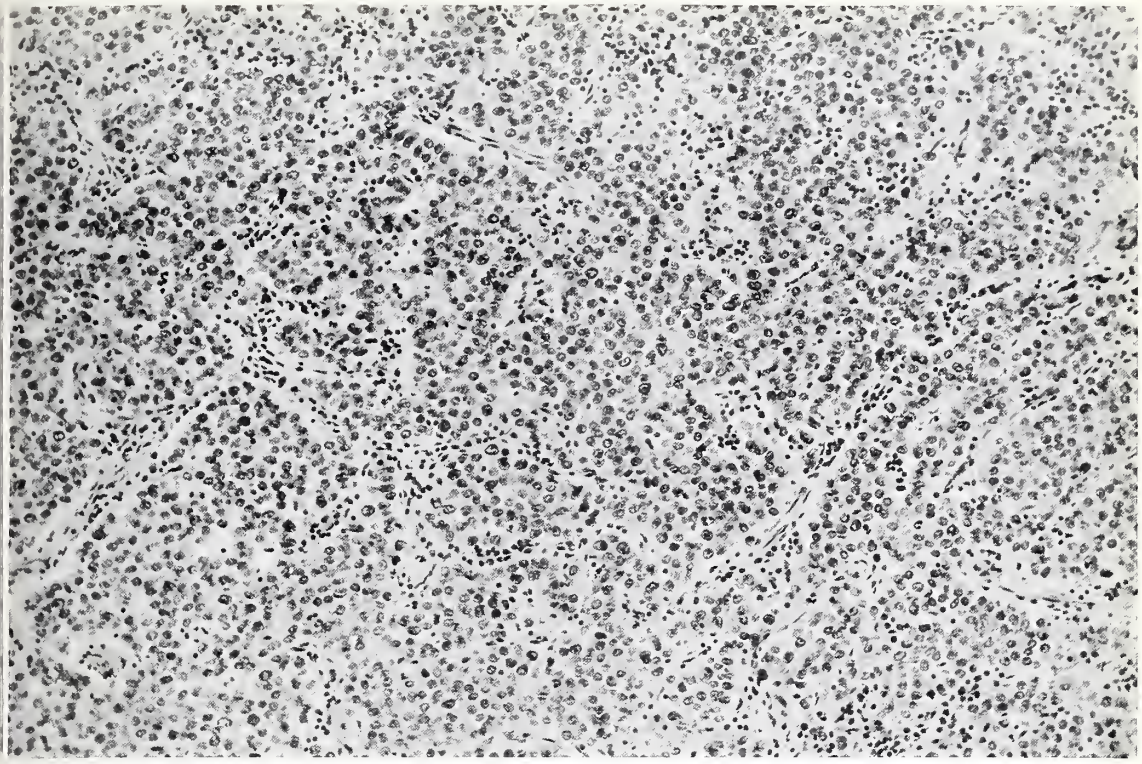

Fig. 34

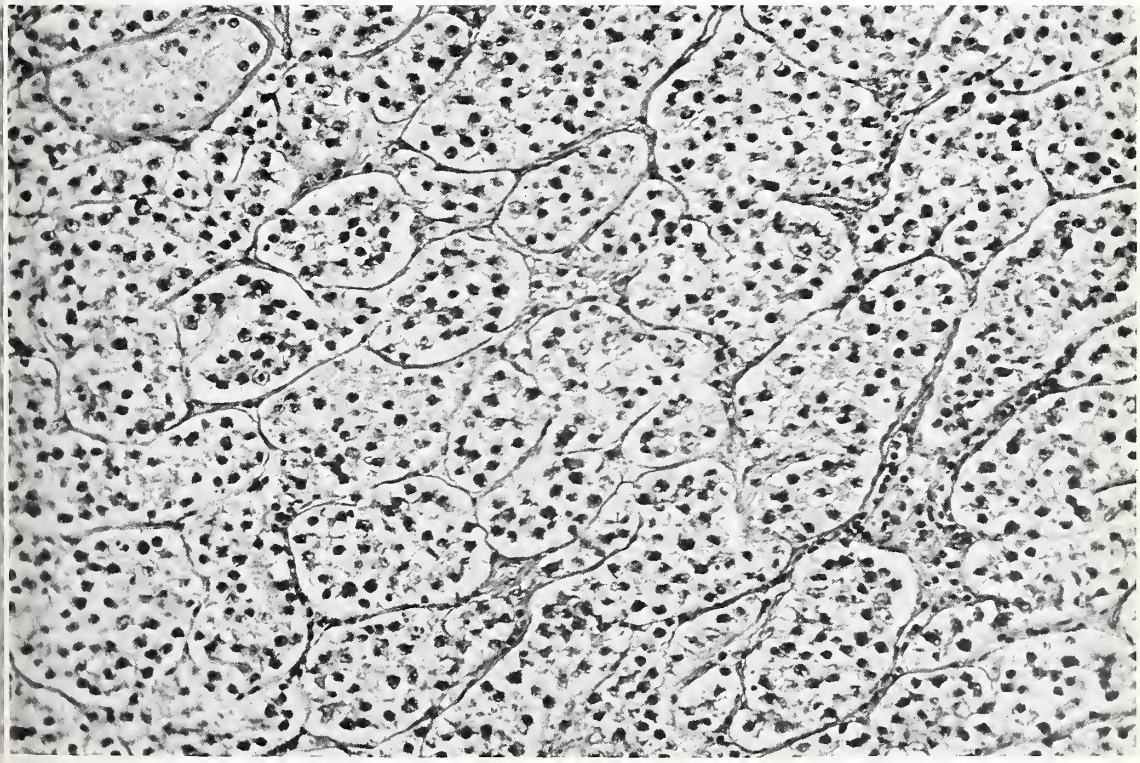

Fig. 35

Figure 36.* Seminoma. Cellular regularity, clear cytoplasm, visible cell borders, and round nuclei with prominent nucleoli are characteristic features. × 545. A. F. I. P. Acc. No. 136322.

Figure 37.* Seminoma showing anaplasia. In spite of cellular irregularity and considerable mitotic activity, the over-all homogeneity and characteristic stromal component make diagnosis certain. × 500. A. F. I. P. Acc. No. 157059.

*From the Armed Forces Institute of Pathology.

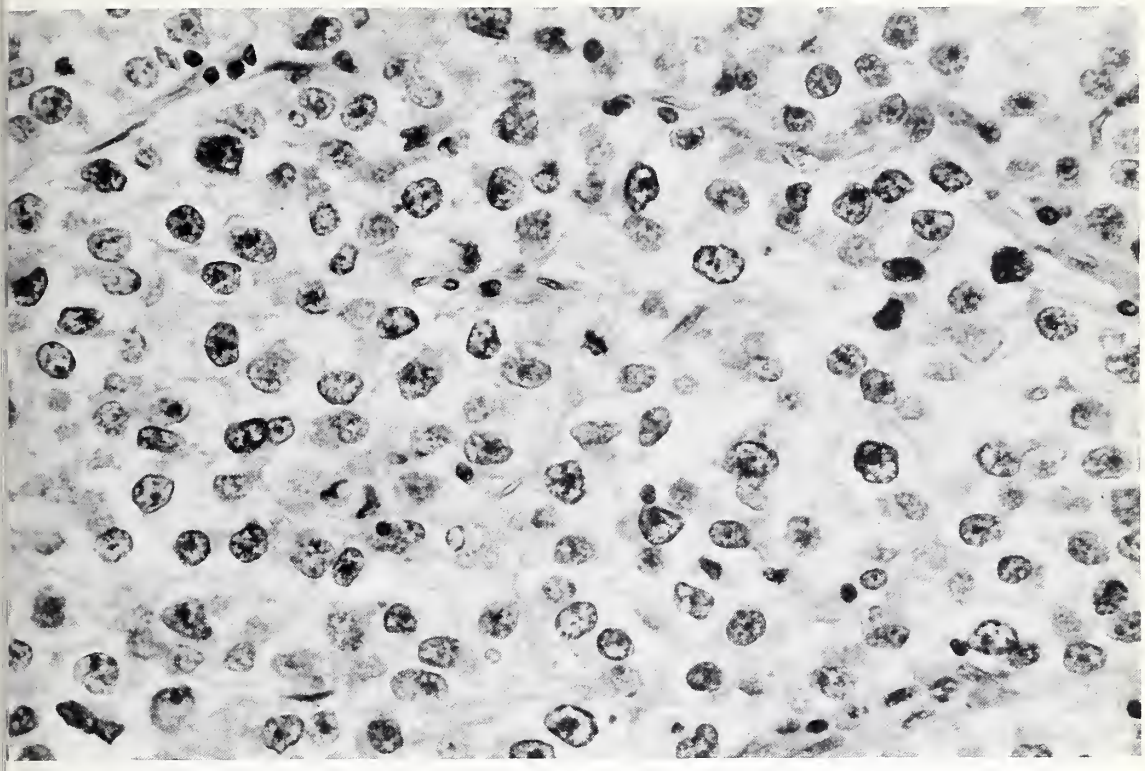

Fig. 36

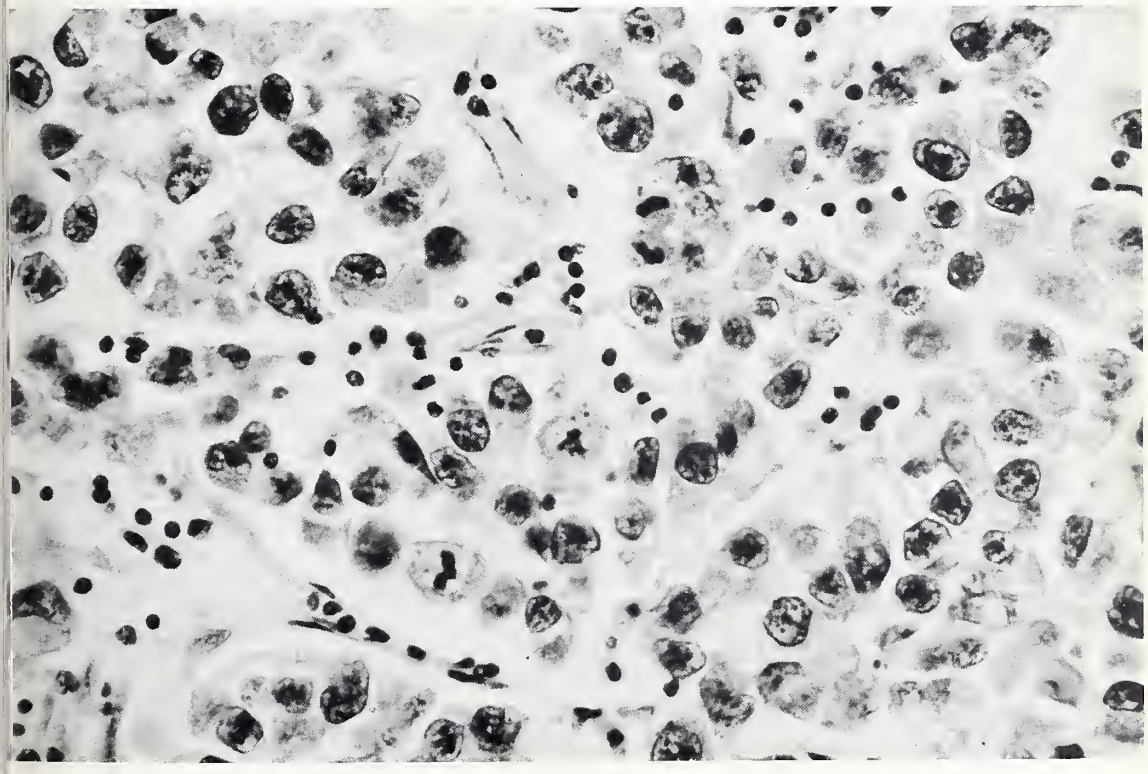

Fig. 37

Figure 38.* Lymphoid stromal response to seminoma. Tumor cells appear as isolated islands of pale-staining cells set in mass of lymphoid tissue. × 114. A. F. I. P. Acc. No. 17416.

Figure 39.* A granulomatous stromal response in seminoma. Cellular response is chiefly lymphoid and histiocytic with some fibroblastic proliferation. Stroma appears to encroach on tumor cells. × 240. A. F. I. P. Acc. No. 86148.

*From the Armed Forces Institute of Pathology.

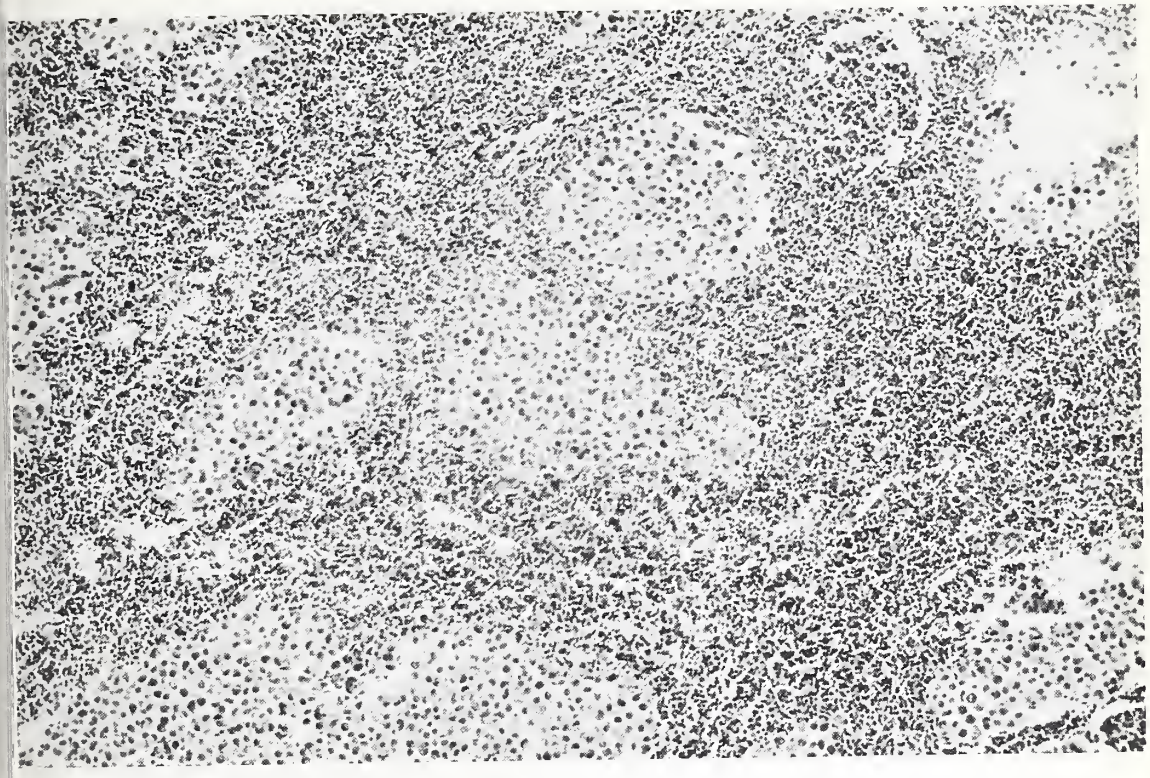

Fig. 38

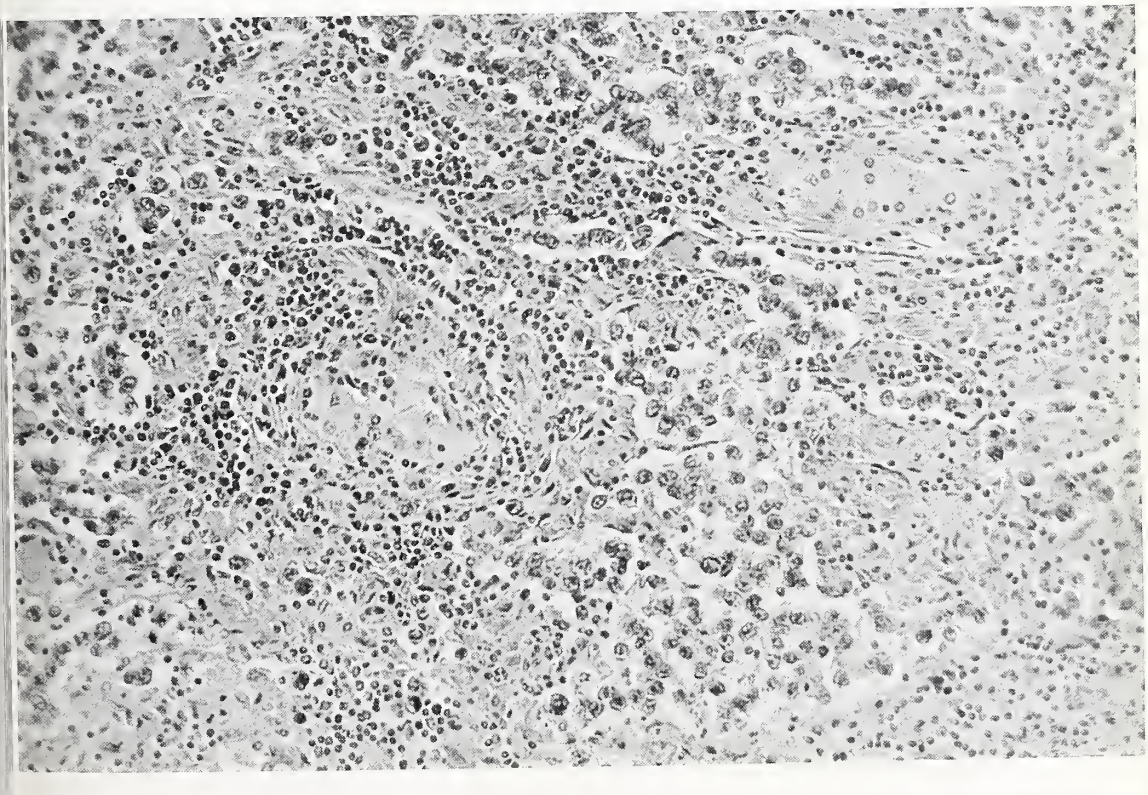

Fig. 39

Figure 40.* Fibrous or scirrhous stromal response to seminoma. Dense collagenous connective tissue appears to be choking out the tumor cells. × 114. A. F. I. P. Acc. No. 96728.

Figure 41.* Syncytial trophoblastic giant cells in seminoma. Large spaces within these giant cells appear to be true vascular channels filled with blood. There is intravascular tumor growth in small vessel in upper left corner. × 205. A. F. I. P. Acc. No. 108597.

*From the Armed Forces Institute of Pathology.

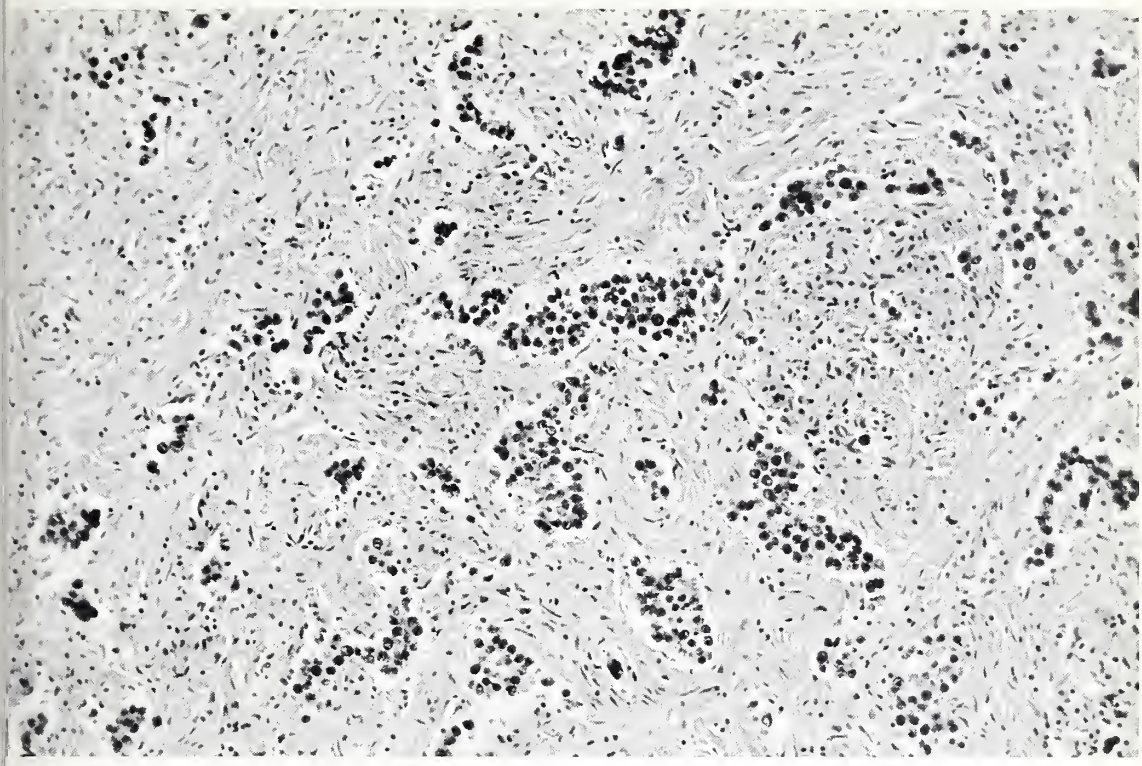

Fig. 40

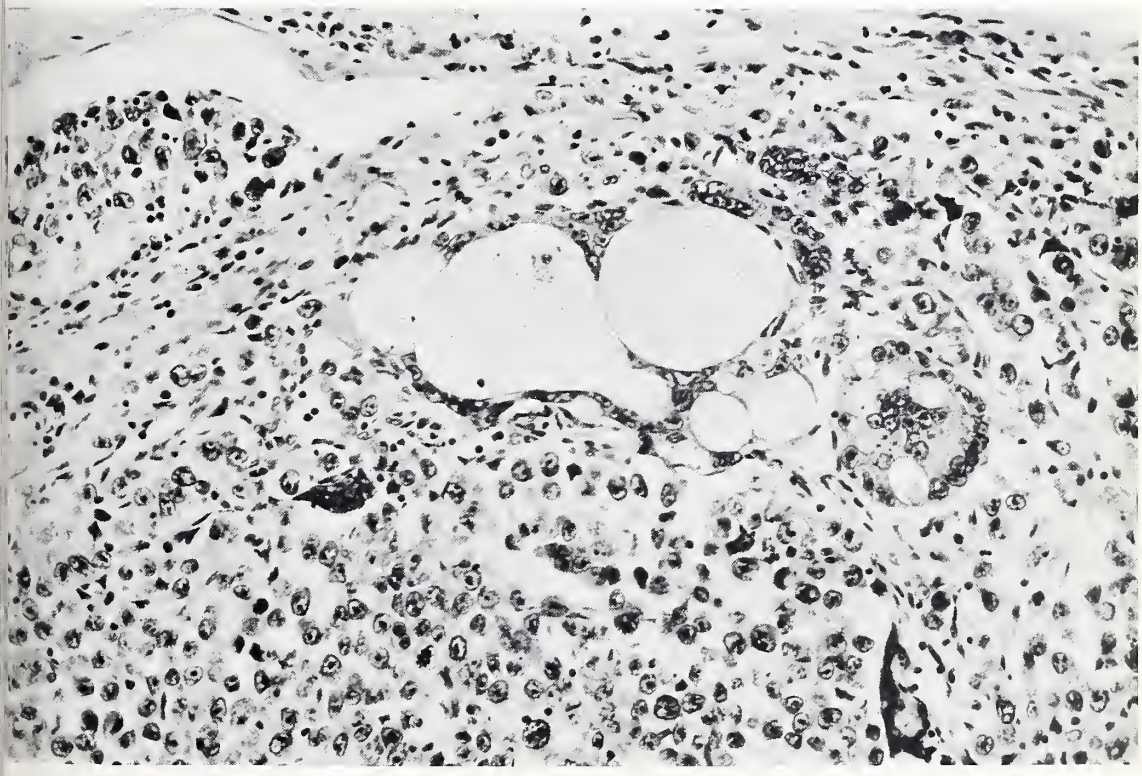

Fig. 41

Figure 42.* Intratubular tumor growth seen in 24 percent of seminomas. The tubules in center of photomicrograph are distended with typical seminoma cells and stand out in contrast to the adjacent atrophic seminiferous tubules. In some instances seminomas may be entirely intratubular without invasion, an example of carcinoma in situ. × 105. A. F. I. P. Acc. No. 166596.

Figure 43.* Extension of seminoma into rete. Typical large clear seminoma cells can be seen lining rete ducts with normal rete epithelium still visible over surface of tumor cells in some places. This invasion appears to be an extension of tumor cells into rete passages, lifting the normal epithelium from the basement membrane as it progresses. × 125. A. F. I. P. Acc. No. 82283.

*From the Armed Forces Institute of Pathology.

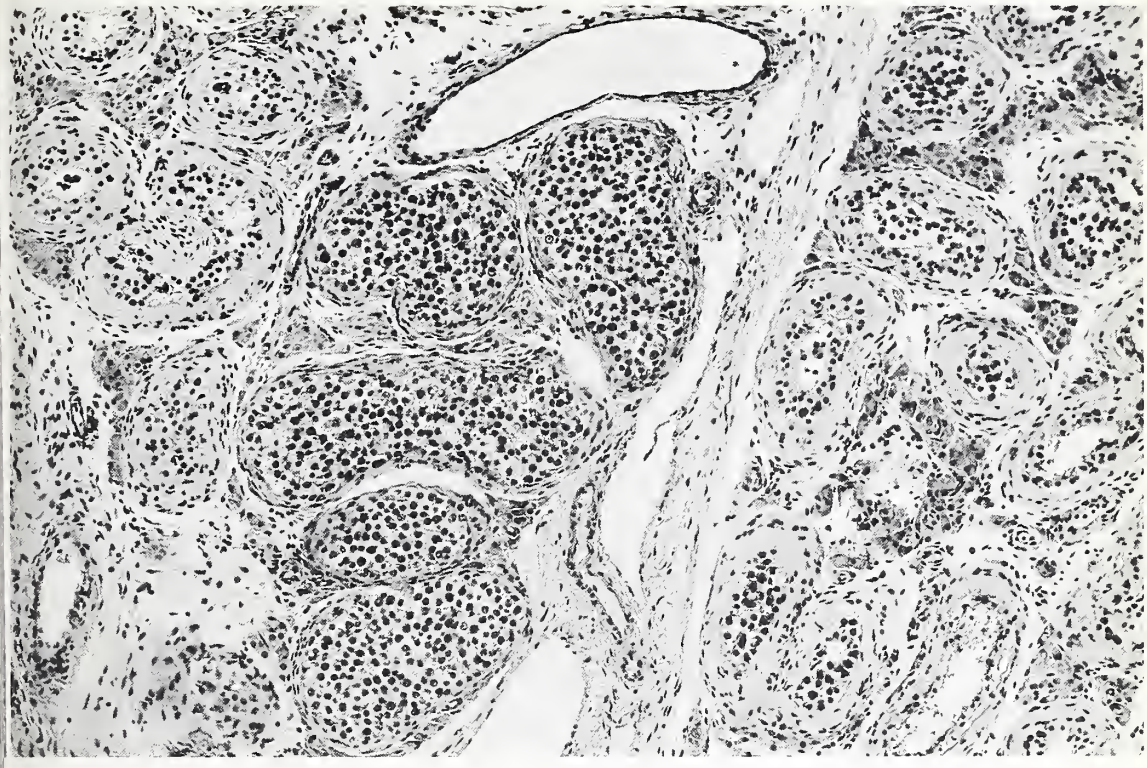

Fig. 42

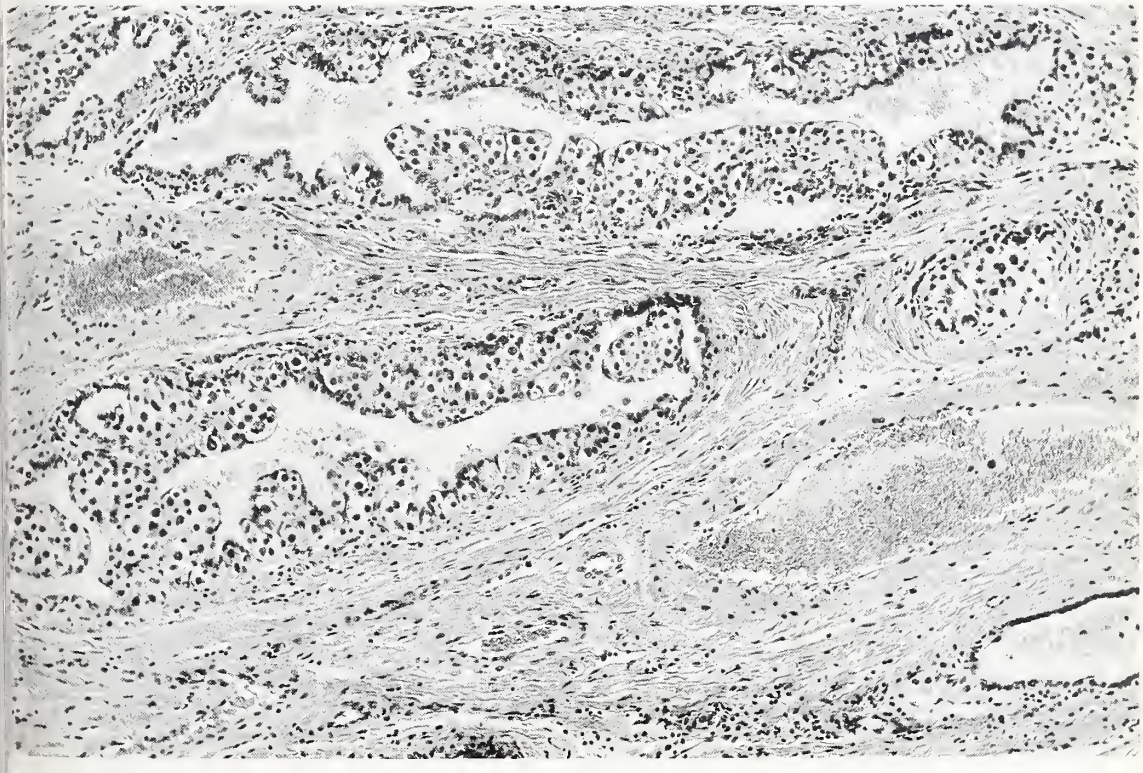

Fig. 43

associated with poor prognosis, but our data did not permit a definite conclusion on this point.

Tumor Group II—Embryonal Carcinoma, Pure or with Seminoma

SYNONYMS AND RELATED TERMS: Adenocarcinoma; cytotrophoblastic carcinoma; embryoma; embryonic carcinoma; embryoplastic carcinoma; teratocarcinoma; teratoid carcinoma.

DEFINITION. The essential element in these tumors is embryonal carcinoma, which is composed of highly malignant, multipotential, anaplastic cells that may be entirely undifferentiated or may show slight differentiation toward somatic or trophoblastic cell forms.

INCIDENCE. Twenty percent of the germinal tumors in the army series were in Group II. In the total population, of somewhat older age distribution, Group II tumors would be expected to make up about 30 percent of germinal tumors.

CLINICAL COURSE AND TREATMENT. Gradual swelling of the testis was the first complaint of about 80 percent of the army patients; rapid swelling was noted in 10 percent; and pain was a complaint of 60 percent. Symptoms were of less than six months duration in two thirds of the patients.

At time of first examination, one third of patients with Group II tumors had clinically demonstrable metastases. Metastases were found in 41 percent of patients with symptoms of more than six months duration and in 25 percent with symptoms of less than six months duration.

Urinary gonadotropin tests were positive in 30 percent of those patients tested preoperatively and in nearly 15 percent postoperatively.

Ninety percent of patients with Group II tumors were treated by orchiectomy, with or without retroperitoneal node dissection, followed by roentgen therapy. Five percent were treated by surgery alone and five percent were inoperable. Mortality for the 95 percent of patients in whom the disease was deemed operable was 59 percent within two years after operation and 65 percent within five years. Deaths were most frequent during the first year, with relatively few deaths after two years (table III). An insignificant number of deaths caused by tumors occurred after five years.

The clinical features of prognostic value were presence of pain, positive urinary gonadotropin tests, and metastases. Patients with pain had a 68 percent 2–year mortality; those without, a 47 percent mortality. Positive urinary gonadotropin tests were associated with an 85 percent 2–year mortality, and negative tests with a 50 percent 2–year mortality. Patients having metastases at time of first examination had a 92 percent 2–year mortality, and those without metastases, a 46 percent. The use of retroperitoneal node dissection seemed to be of some value in these cases. Of 32 cases so treated, 44 percent died within two years, while of 125 cases treated without node dissection, 63 percent died within two years.

GROSS. Group II tumors, embryonal carcinomas, are the smallest ger-

minal tumors, averaging 49 cc. in volume with 40 percent less than 20 cc. They may replace part or all of the testis and frequently distort the capsular surface. About one quarter will have invaded epididymis or cord before they are discovered. Size of tumor in army patients was not correlated with clinical course; but the presence of extratesticular extension was associated with an 82 percent 2–year mortality, while in the absence of extension patients had a 47 percent 2–year mortality.

On section, the tumors appear variegated, having a granular to smooth, gray-white surface with numerous areas of hemorrhagic necrosis (figs. 44, 45).

Distribution of metastases determined from 68 autopsies was as follows: periaortic and iliac lymph nodes, 96 percent; each lung, 84 percent; liver, 80 percent; pleura, 46 percent; bones of trunk, 21 percent; and gastrointestinal tract, 18 percent (figs. 46, 47).

MICROSCOPIC. The essential component of Group II tumors is embryonal carcinoma. As indicated in the section on Classification (see page 50), embryonal carcinoma is as much a conceptual as a morphologic entity. The completely undifferentiated form is made up of large, pleomorphic, anaplastic cells, with homogeneous, amphophilic cytoplasm and without obvious cell borders (figs. 48, 49). The nuclei are irregularly oval with a light chromatin pattern and one or more prominent nucleoli. Numerous mitotic figures are characteristic. The stromal reaction is variable: in some instances it is scirrhous and in others it is absent entirely. There is, however, no regular stromal pattern as in seminomas. In areas of hemorrhagic necrosis all tumor structure is lost, in contrast to the ischemic necrosis with ghost cells seen in seminomas.

In the embryonal carcinomas showing early somatic differentiation there is an organization of some of the cells into layers resembling primitive epithelium and reticulated masses suggesting embryonic mesoderm (figs. 50–52, 54, 55). We have arbitrarily classified such tumors as embryonal carcinoma so long as no recognizable tissues are formed. This variety of embryonal carcinoma has frequently been called testicular adenocarcinoma. It is, however, not a distinct entity, but a transitional step from the totally undifferentiated embryonal carcinoma to the typical teratoma.

Embryonal carcinomas showing early trophoblastic differentiation usually contain typical dark syncytial trophoblastic elements and undifferentiated cells (fig. 53). These two elements bear an inconstant relation to one another, and chorionic villi are absent.

Any one, or more frequently two or all three, of these patterns may be found in a single tumor. Occasional embryoid bodies bearing at least superficial resemblance to embryos one or two weeks old are seen in these tumors (figs. 56, 57). Whether these represent true parthenogenetic changes is debatable, but their presence suggests intriguing possibilities.

Figure 44.* Embryonal carcinoma, testis. Small, poorly demarcated, hemorrhagic, infiltrating tumor is seen in upper pole of testis. Hemorrhage into small tumors is more common in embryonal carcinomas and choriocarcinomas than in seminoma. A. F. I. P. Acc. No. 232746.

Figure 45.* Embryonal carcinoma with slight teratoid differentiation, testis. Testis is completely replaced and enlarged by tumor. Variegated cut surface, foci of hemorrhagic necrosis, and extension through tunica albuginea differentiate the gross appearance of this tumor from that of seminoma. A. F. I. P. Acc. No. 216070–1.

*From the Armed Forces Institute of Pathology.

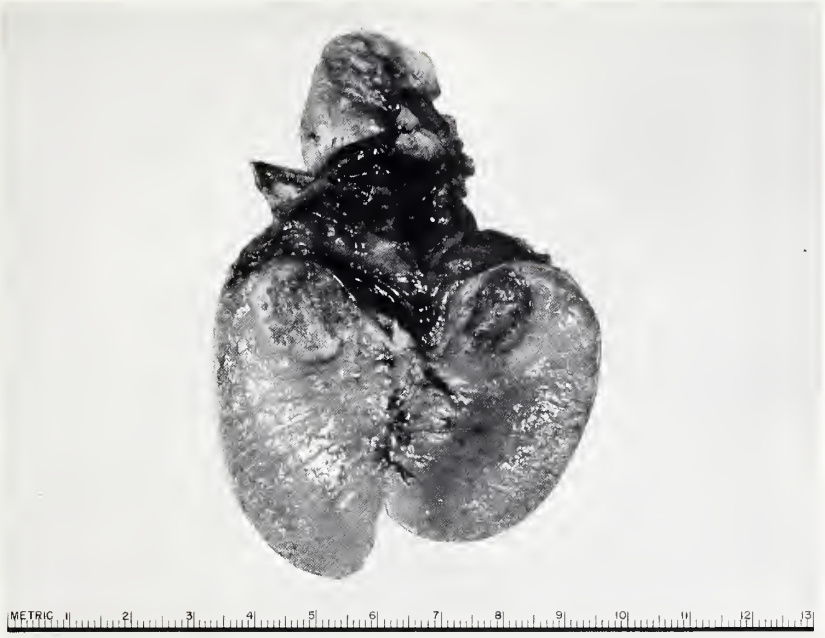

Fig. 44

Fig. 45

Figure 46.* Periaortic metastases from embryonal carcinoma of testis. Metastatic spread via lymphatics to regional nodes along the aorta up to the renal pedicles is the most common route of dissemination of testicular tumors. Large mass of tumor surrounds aorta and renal pedicle. A. F. I. P. Acc. No. 212003–1.

Figure 47.* Mediastinal and pulmonary metastases from embryonal carcinoma of testis. Once the abdominal lymphatics and lymph nodes are saturated with metastic tumor, spread to the mediastinum is frequent. Pulmonary involvement by tumor is probably blood-borne, although retrograde lymphatic spread from mediastinum is possible. A. F. I. P. Acc. No. 108551–1.

*From the Armed Forces Institute of Pathology.

Fig. 46

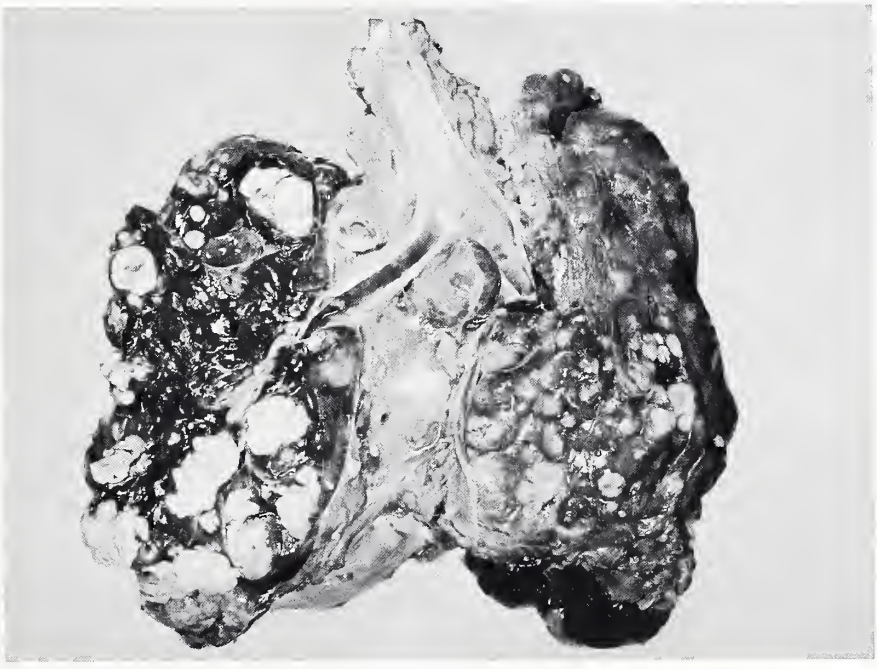

Fig. 47

Figure 48.* Embryonal carcinoma, solid undifferentiated type. Cellular irregularity, presence of flattened dark cells near periphery of tumor lobules, invasion of stroma, and absence of definite stromal response or pattern are characteristic. × 115. A. F. I. P. Acc. No. 153133.

Figure 49.* Embryonal carcinoma, undifferentiated type. Cellular anaplasia, absence of cell borders, eosinophilic or amphophilic nature of cytoplasm, large bizarre nuclei, and much mitotic activity differentiate this tumor from seminoma. × 655. A. F. I. P. Acc. No. 136327.

*From the Armed Forces Institute of Pathology.

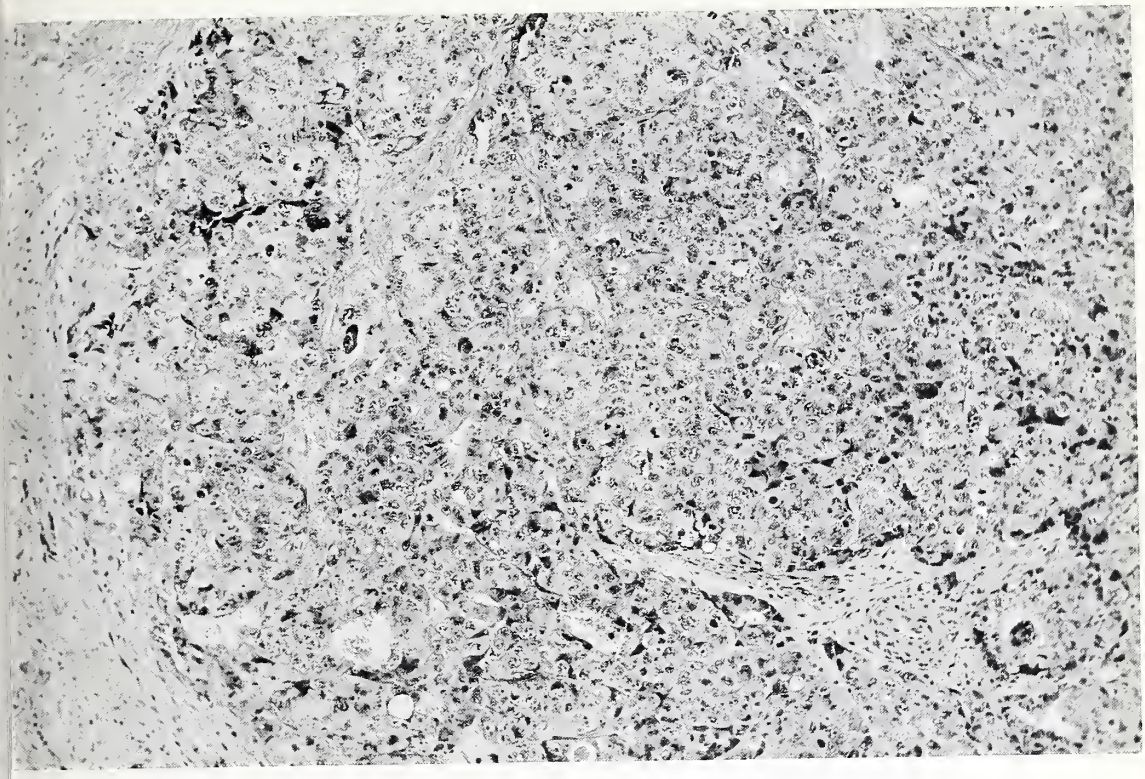

Fig. 48

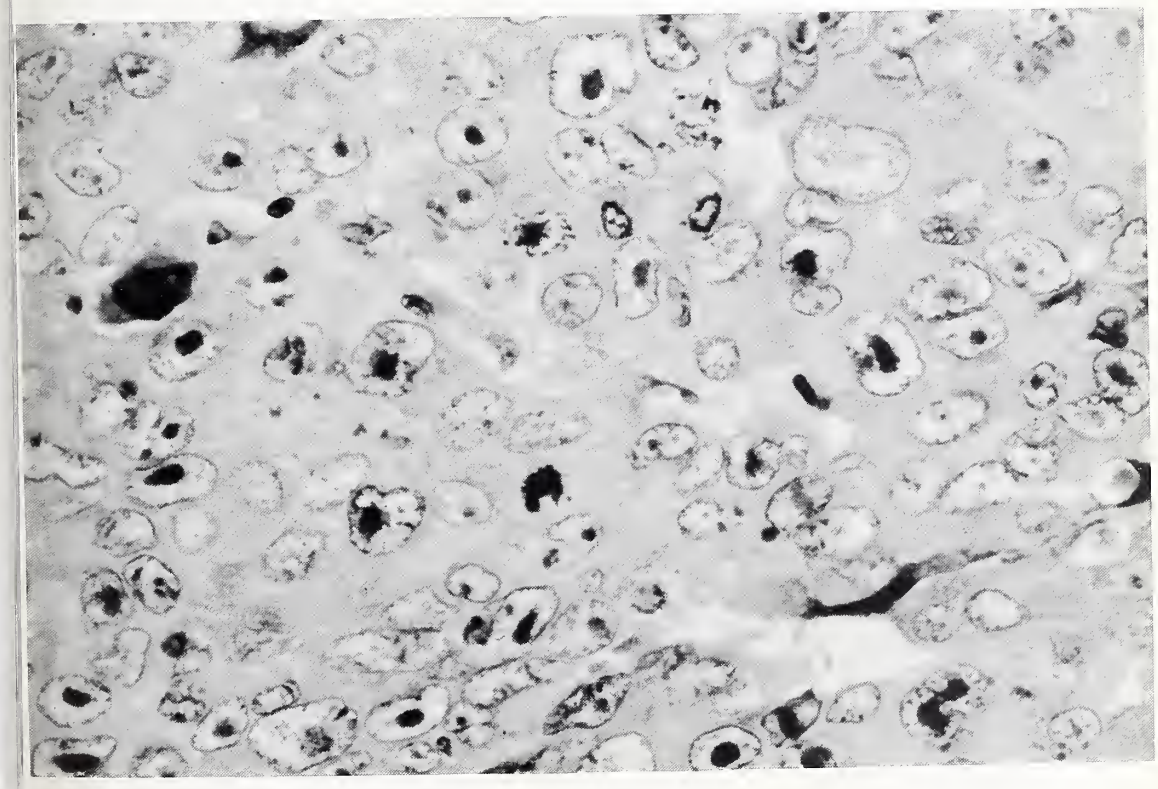

Fig. 49

Figure 50.* Embryonal carcinoma from same case as figure 49, showing early epithelial differentiation. Columnar epithelium is forming over surface of undifferentiated tumor cells. Foci of epithelial differentiation in predominantly undifferentiated embryonal carcinomas are common. × 555. A. F. I. P. Acc. No. 136327.

Figure 51.* Embryonal carcinoma, mesodermal type. The reticulated connective tissue type of cellular arrangement is reminiscent of embryonic mesenchyme. The term carcinoma referring to a mesodermal growth is, while inaccurate, probably preferable to coining a new name. Classifying this tumor type with the undifferentiated and epithelial forms of embryonal carcinoma indicates its origin and histogenesis. From a clinical standpoint, this terminology is desirable, since all varieties of embryonal carcinoma have a similar prognosis. × 605. A. F. I. P. Acc. No. 116232.

*From the Armed Forces Institute of Pathology.

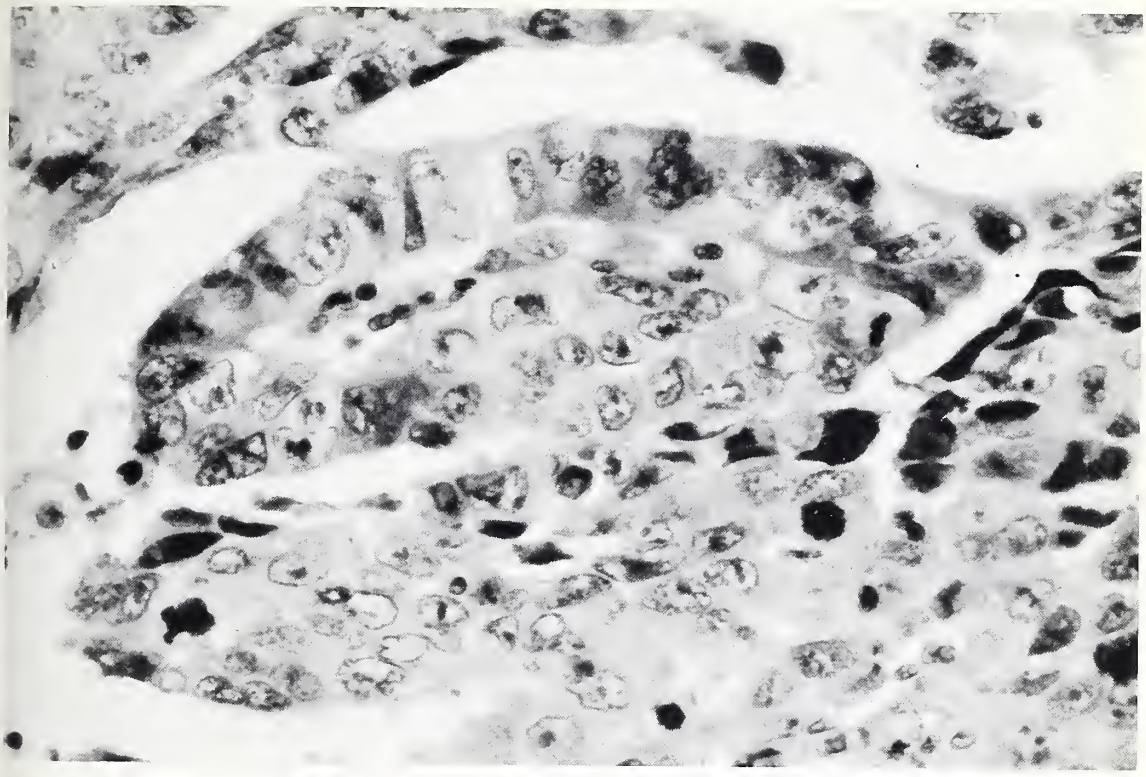

Fig. 50

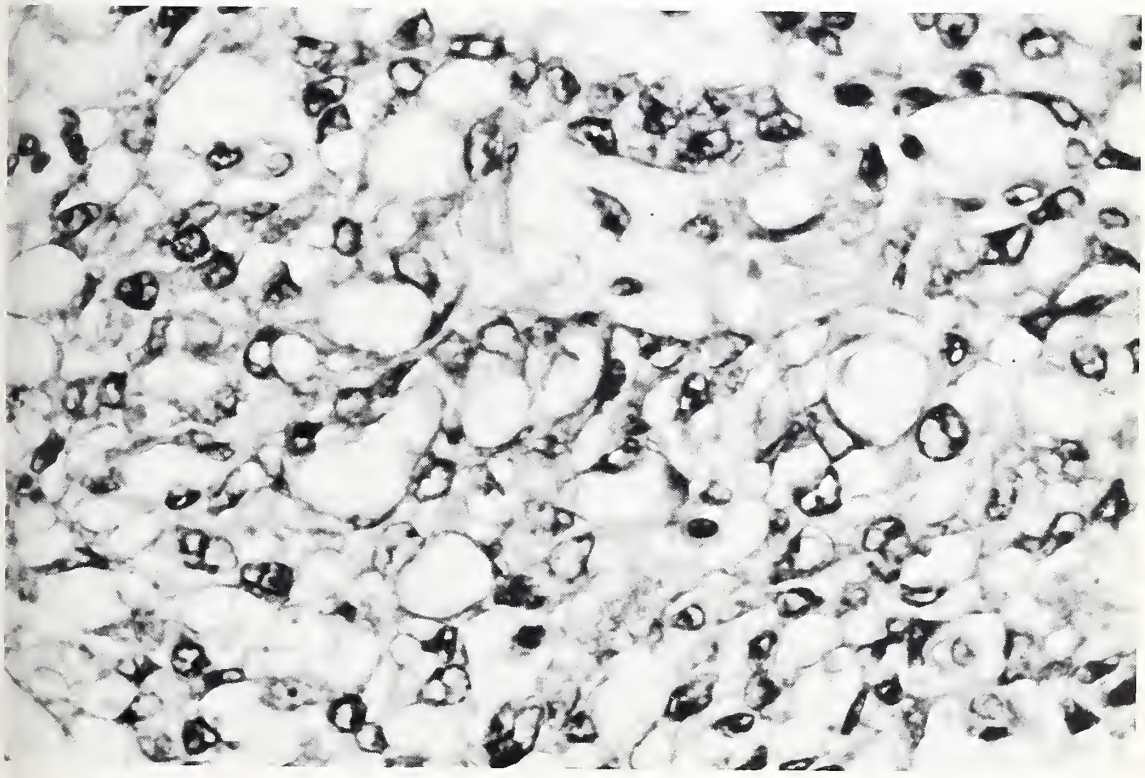

Fig. 51

Figure 52.* Embryonal carcinoma showing epithelial and mesodermal differentiation. Dark cuboidal to columnar epithelium covers mesodermal tissue in right side of photomicrograph. Papillary epithelial growth is seen at left. × 280. A. F. I. P. Acc. No. 105487.

Figure 53.* Embryonal carcinoma, trophoblastic type. Smudgy dark giant cells are developing within and over the free surfaces of the tumor. The resemblance of the giant cells to syncytial trophoblast and the remaining cells to cytotrophoblast is apparent. Transitions from undifferentiated embryonal carcinoma through intermediate stages, such as seen here, to well developed choriocarcinoma are not uncommon in one tumor. × 260. A. F. I. P. Acc. No. 192599.

*From the Armed Forces Institute of Pathology.

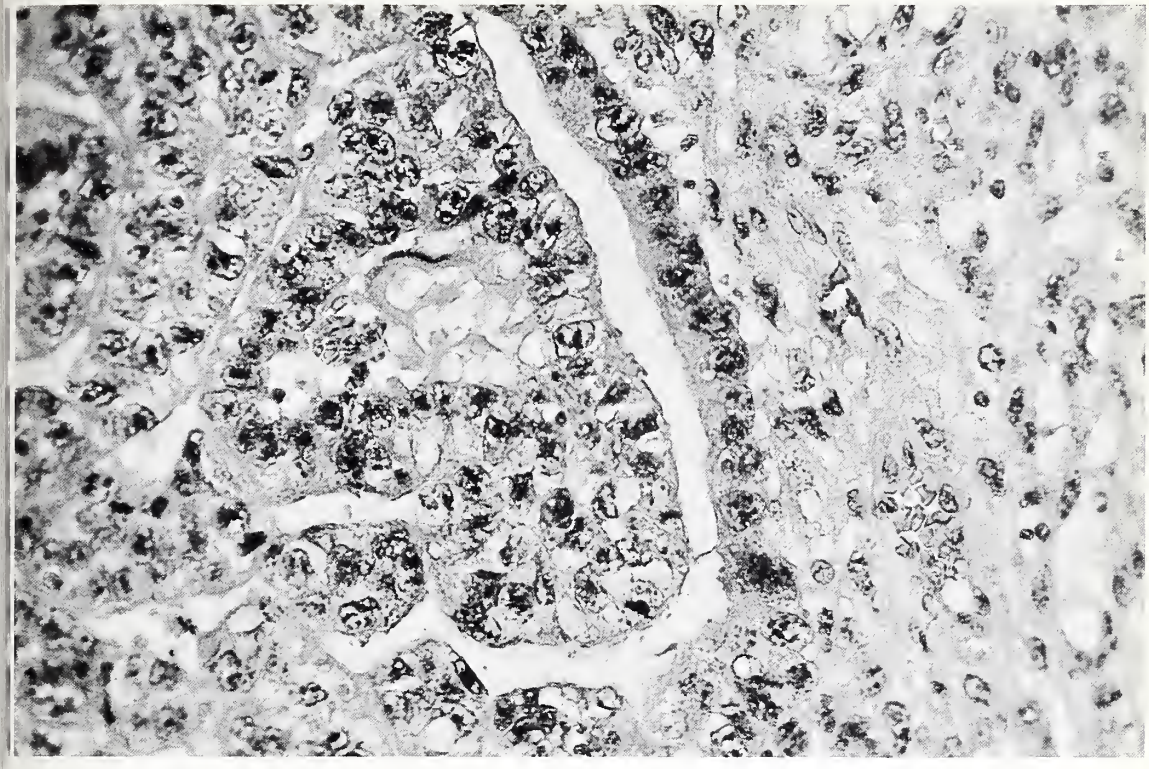

Fig. 52

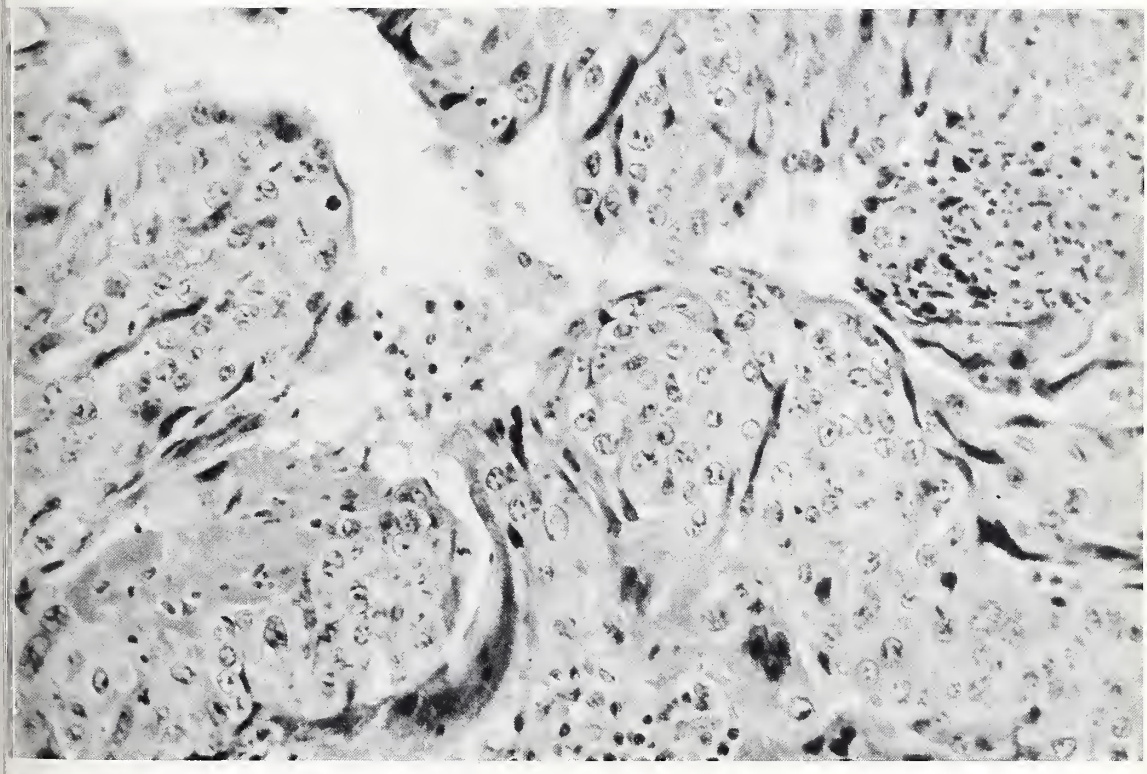

Fig. 53

Figure 54.* Well developed epithelial form of embryonal carcinoma. This form has frequently been called adenocarcinoma of testis. The development of this adenomatous pattern does not alter prognosis from that for less differentiated embryonal carcinoma. × 155. A. F. I. P. Acc. No. 154376.

Figure 55.* Embryonal carcinoma with unusual pattern. These double-layered epithelial structures, which are usually found mixed with other types of embryonal carcinoma, have been likened to mesonephric structures or neural tubes. The development of any form of embryonal tissue can be expected in these near totipotential tumors. × 125. A. F. I. P. Acc. No. 102966.

*From the Armed Forces Institute of Pathology.

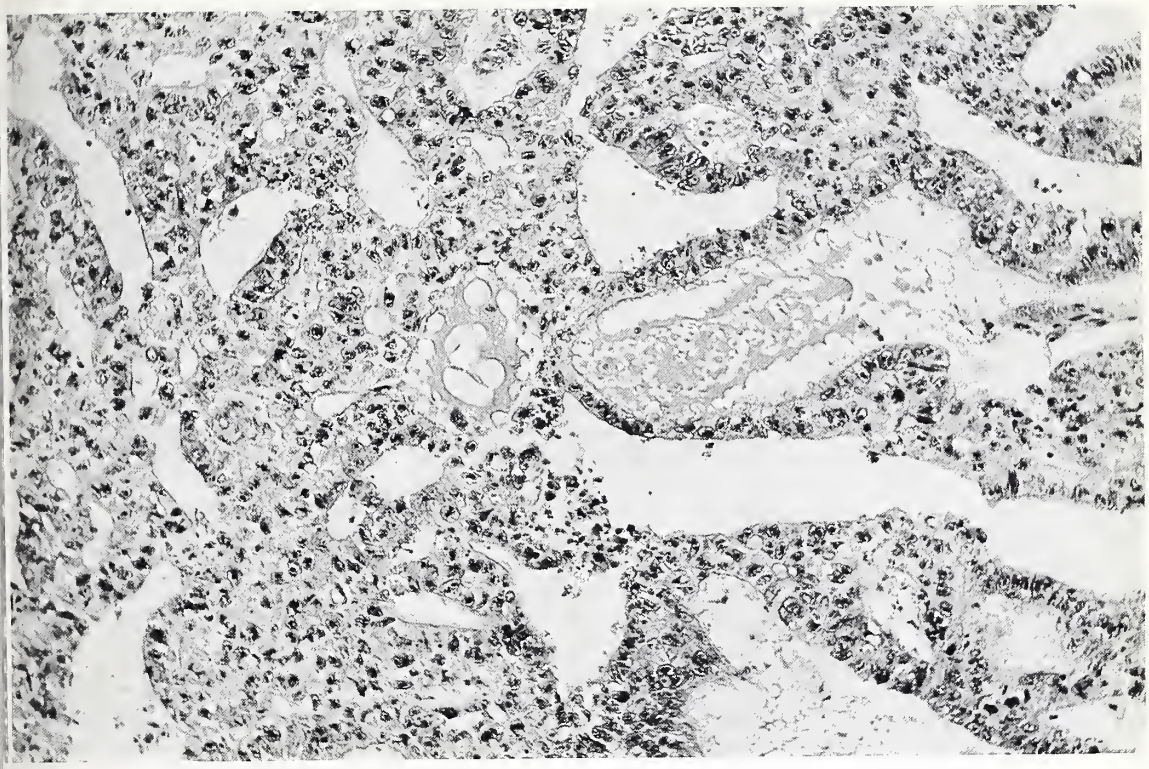

Fig. 54

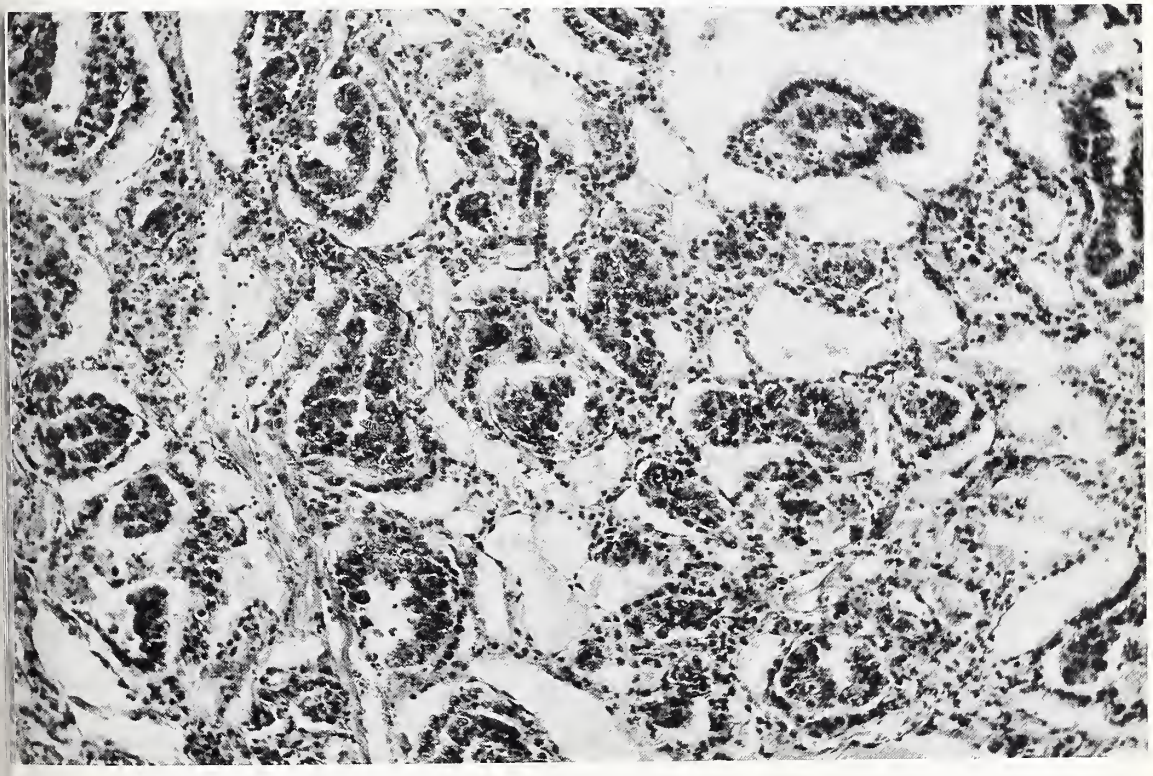

Fig. 55

Figure 56.* Embryoid body in embryonal carcinoma. Structure resembling an embryonic disc one to two weeks old can be seen at left and single giant cell suggesting trophoblast at right. Embryoid bodies are usually found in tumors composed of embryonal carcinoma and teratoma. In spite of much controversy, the true nature of these structures is still undecided. × 435. A. F. I. P. Acc. No. 150834.

Figure 57.* Embryoid body showing prominent embryonic disc at center with amnion above and entoderm below. × 605. A. F. I. P. Acc. No. 127389.

*From the Armed Forces Institute of Pathology.

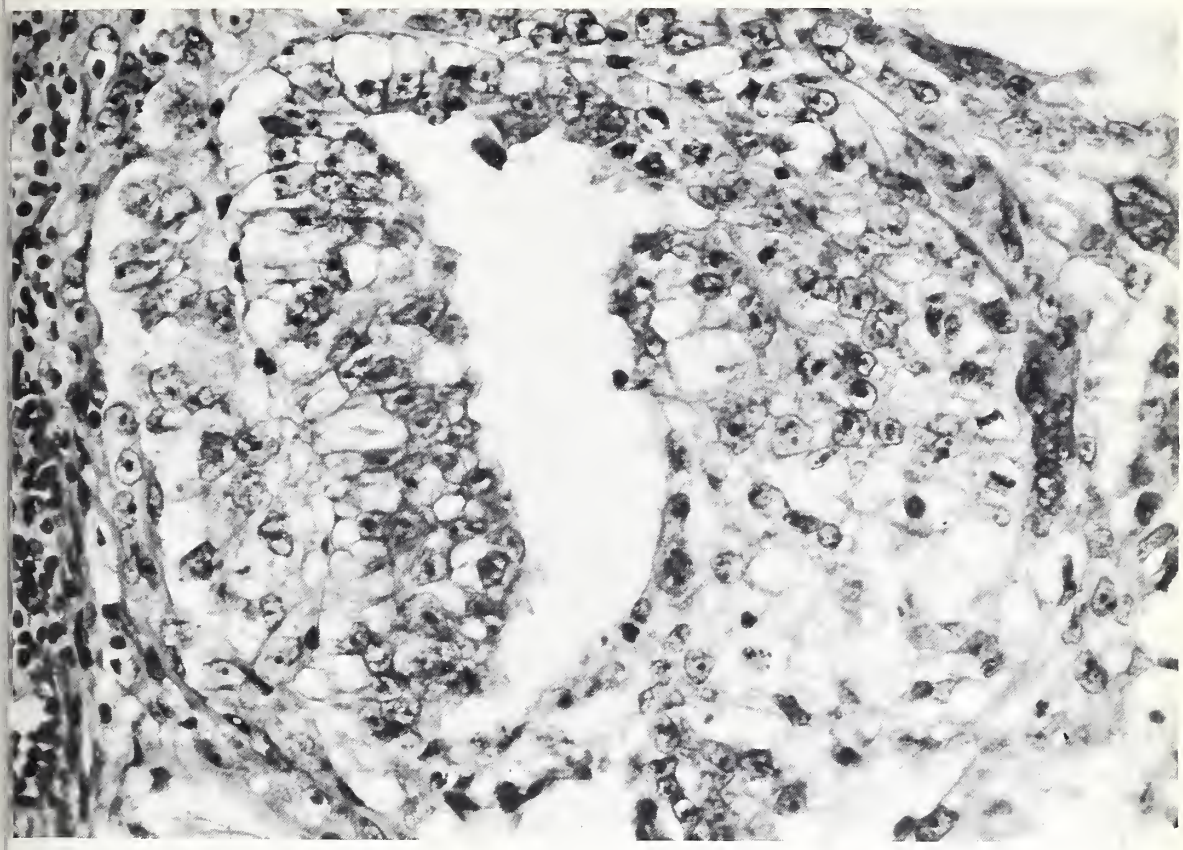

Fig. 56

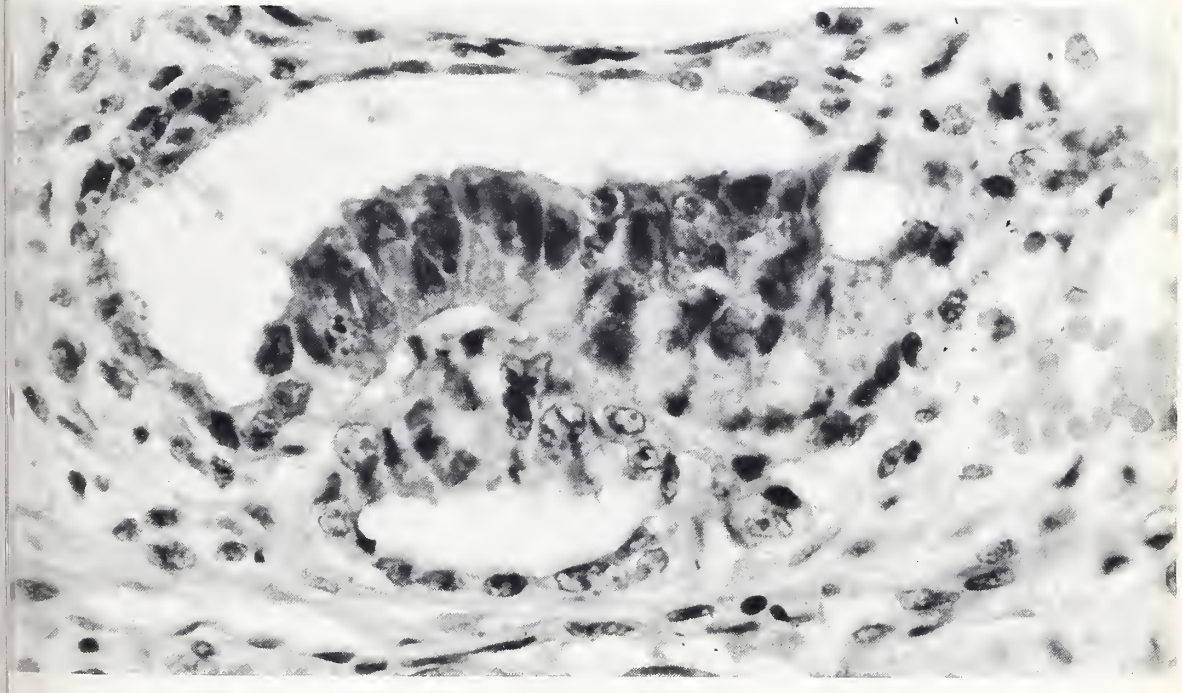

Fig. 57

Figure 58.* Junction of embryonal carcinoma, upper left, and seminoma, lower right. Although these two tumors often coexist in the same testis, intermingling is unusual, and when it is found, there are no intermediate transition stages, but rather the appearance of two distinctly different tumors in juxtaposition. × 435. A. F. I. P. Acc. No. 95455.

Figure 59.* Junction of undifferentiated embryonal carcinoma and relatively well differentiated columnar epithelium in lining of this cystic space. Transition of undifferentiated tumor cells to early differentiated forms is not unusual in embryonal carcinomas with associated teratoma. × 260. A. F. I. P. Acc. No. 114970.

*From the Armed Forces Institute of Pathology.

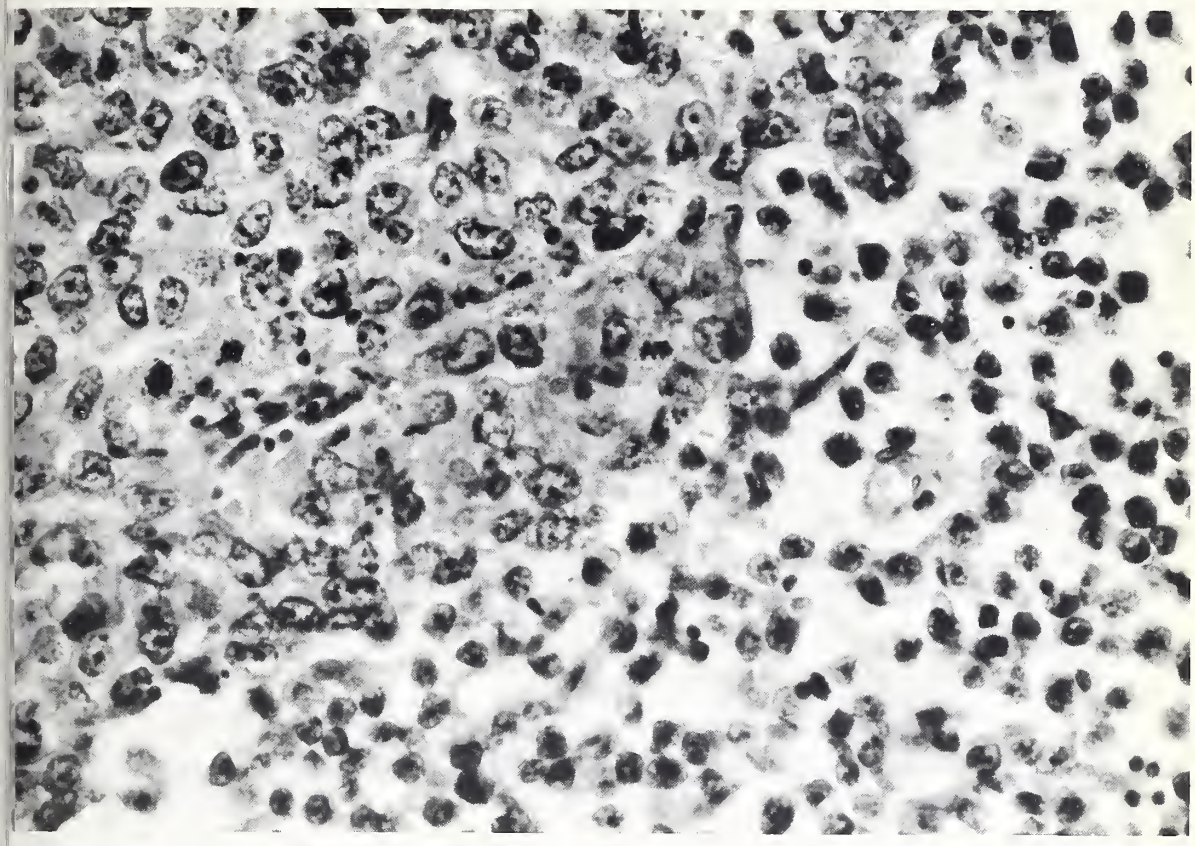

Fig. 58

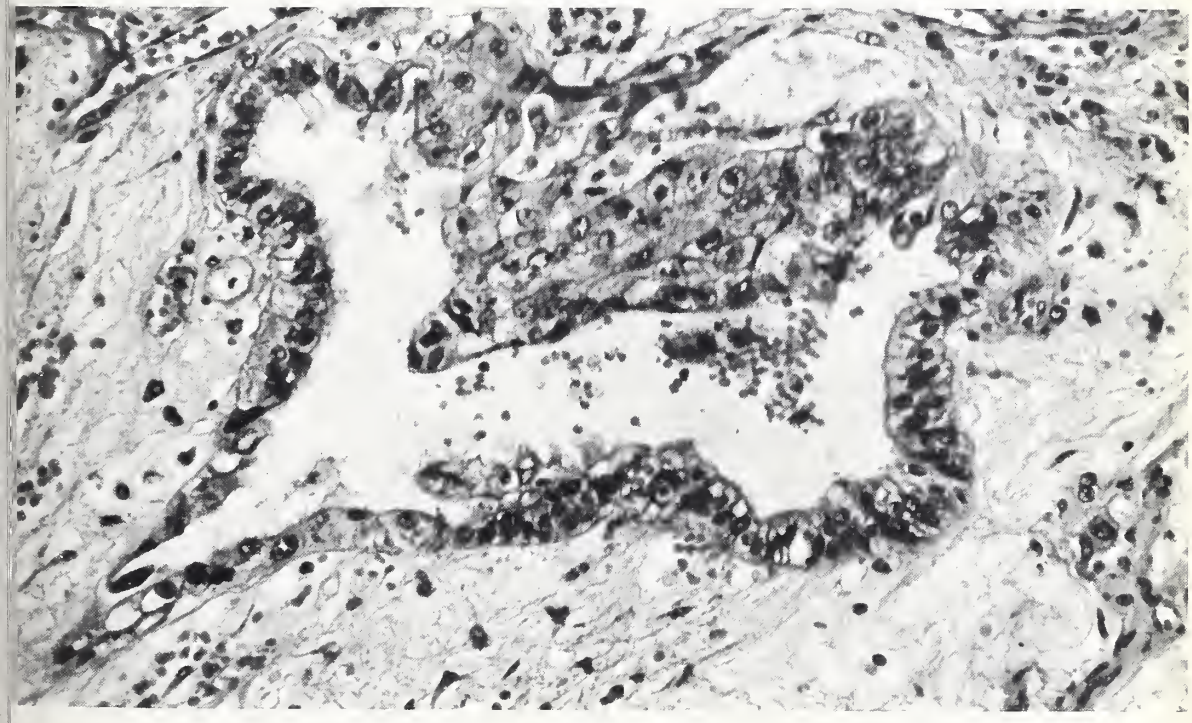

Fig. 59

The seminomatous elements found in some of the Group II tumors are identical histologically to the pure seminomas in Group I. When seminoma and embryonal carcinoma coexist, there are no intimate mixtures or suggested transition zones (fig. 58). However, frequently the seminoma exists in the form of small satellite nodules about a larger embryonal carcinoma.

The microscopic structure of metastases in 74 of the army cases revealed embryonal carcinoma in 96 percent, teratoma in 8 percent, and choriocarcinoma in 5 percent.

The presence of vascular invasion was again associated with poor prognosis. The tumors with vascular invasion had a 74 percent 2–year mortality, and those without invasion, a 36 percent 2–year mortality. The tumors associated with hyperplasia of interstitial cells had a 2–year mortality of 81 percent, and those with normal interstitial cells, a mortality of 49 percent.

Tumor Group III—Teratoma, Pure or with Seminoma

SYNONYMS AND RELATED TERMS: See Fascicle 9, "Teratomas."

DEFINITION. The essential element in Group III tumors is teratoma, which is made up of recognizable somatic tissues corresponding to either fetal or adult stages of development.

INCIDENCE. Group III constituted nine percent of the germinal tumors in the army series. Incidence in all age groups in this series was practically uniform.

CLINICAL COURSE AND TREATMENT. Chief complaints were gradual swelling of the testes (74 percent) and pain (43 percent). About one third of patients had noticed symptoms for more than six months before seeking medical aid. At time of first examination 24 percent of patients had clinically demonstrable metastases.

Twenty-eight percent of patients with Group III tumors tested preoperatively had positive urinary gonadotropin.

Treatment of the Group III tumors in the army series consisted of surgery followed by radiation in 70 percent of cases and surgery alone in 26 percent.

Mortality rates for the 96 percent of the cases operated on were 26 percent within two years after operation and 29 percent within five years (table II). The peak mortality occurred during the first year, and no deaths were observed after four years (table III).

The only clinical feature of prognostic value was presence of pain, which was associated with a 40 percent 2–year mortality, while cases without pain had an 18 percent 2–year mortality. The 10 patients treated by retroperitoneal node dissection had a 10 percent 2–year mortality, while those treated with less extensive surgery had a 26 percent rate. The duration of symptoms was of no prognostic value in this tumor group.

GROSS. Group III tumors vary considerably in size, about one third being less than 20 cc. and nearly one fourth greater than 100 cc., with an average

of 70 cc. They replace part, or more often all, of the testis and usually result in a nodular, irregular distortion of the capsule. Only 6 percent of these tumors in the army series showed extension beyond the testicular capsule; however, those with extension had a 57 percent 2-year mortality, while those without had a 15 percent 2-year mortality. The size of the tumor bore no relation to the prognosis.

Teratomas cut with irregularly increased resistance. The cut surfaces are honeycombed with cystic spaces of varying sizes that are filled with thin or gelatinous fluid (fig. 60). Frequent islands of firm, translucent cartilage and occasional spicules of bone can be identified in the firm stroma. Necrosis and hemorrhage are rare in these tumors.

In 19 autopsies, the distribution of metastases was as follows: periaortic and iliac lymph nodes, 100 percent; liver, 83 percent; each lung, 72 percent; bones of trunk, 36 percent; pleura, 35 percent; and intestine, 25 percent.

MICROSCOPIC. The essential element in the Group II tumors is teratoma. Histologically, the teratoma is composed of a chaotic array of various differentiated tissues corresponding to either fetal or adult stages in development (figs. 61–68). In the army patients, almost all of the tissues of the body were represented in the hodgepodge of teratoid structures. Frequently the differentiation went beyond the tissue level, and organoid dvelopment could be recognized. The most common tissues in the teratomas were: **ectoderm**—squamous epithelium with or without keratinization and neuroglial tissue; **entoderm**—gastrointestinal epithelium, respiratory epithelium, and mucous glands; and **mesoderm**—smooth muscle, cartilage, and lymphoid tissue. Organoid development was most often represented by intestinal structures containing mucosa, submucosa, and muscularis and bronchial structures containing ciliated epithelium, cartilage, and smooth muscle. In the neuroglial tissue, ependymal canals were not infrequent.

There was no evidence of over-all or axial organization of the tissues and organs of the teratoma into a total organism. This fact has been used by Willis as an argument against the germinal origin of teratomas (see Fascicle 9, "Teratomas"). On the contrary, it seems reasonable that the reproduction of almost all of the somatic tissues in the testicular teratomas is sufficient evidence of their totipotentiality or germinal origin. More could hardly be expected of a neoplastic germ cell.

When seminomas were found associated with teratomas, the former were frequently satellite nodules about the teratoma. There was little or no intimate association of these two elements.

Microscopic examination of metastases from 16 Group III tumors showed embryonal carcinoma in 63 percent, teratoma in 63 percent, and choriocarcinoma in 25 percent. The dissemination of embryonal carcinoma and chorio-

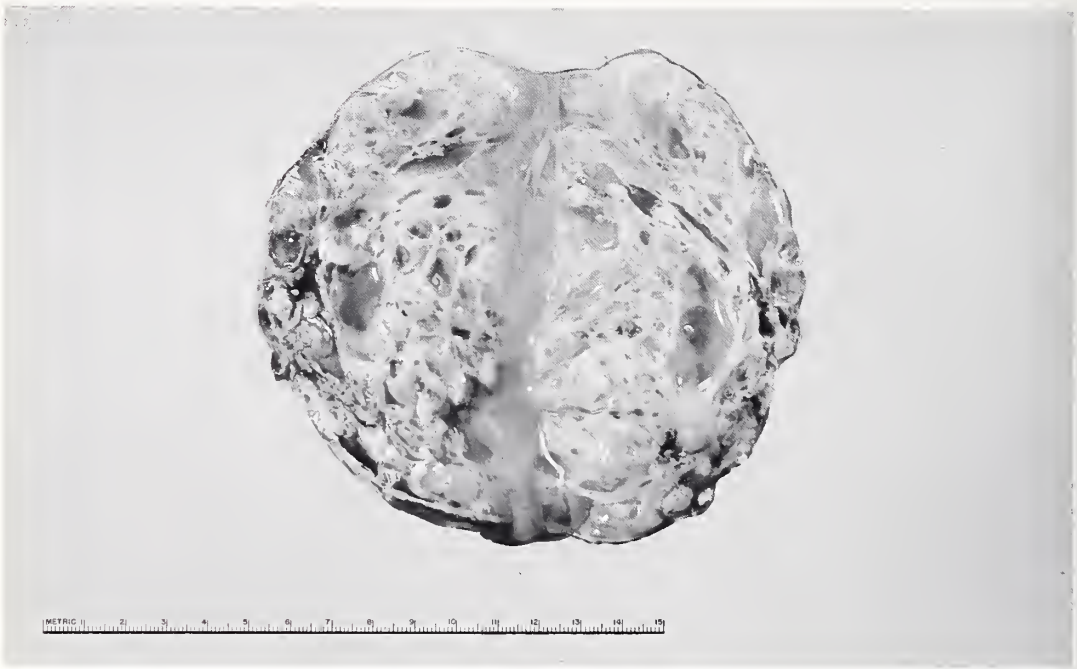

Figure 60. Testicular tumor predominantly teratoma. Multicystic structure is characteristic of teratomas. Cyst contents are mucinous or caseous, depending upon entodermal or ectodermal character of epithelial lining. Islands of hyaline cartilage can frequently be identified in the tumor sfroma. (From the Armed Forces Institute of Pathology.) A. F. I. P. Acc. No. 105411.

Figure 61.* Well differentiated ciliated epithelium apparently formed in the midst of undifferentiated tumor cells. × 705. A. F. I. P. Acc. No. 141374.

Figure 62.* Early cartilage forming in cellular connective tissue of teratoma. Islands of cartilage appear to enlarge by apposition of adjacent cells which take on characteristics of chondroblasts. Typical cartilaginous matrix is present. Columnar epithelium, such as is seen in lower left, is frequently associated with cartilage. × 185. A. F. I. P. Acc. No. 108551.

*From the Armed Forces Institute of Pathology.

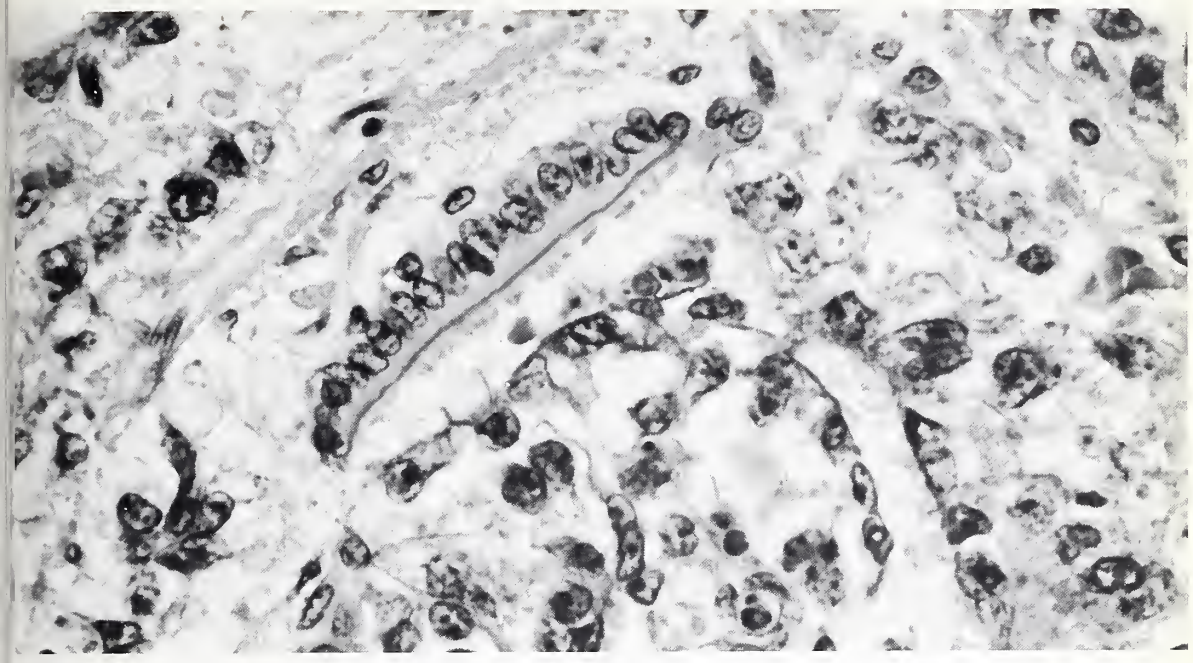

Fig. 61

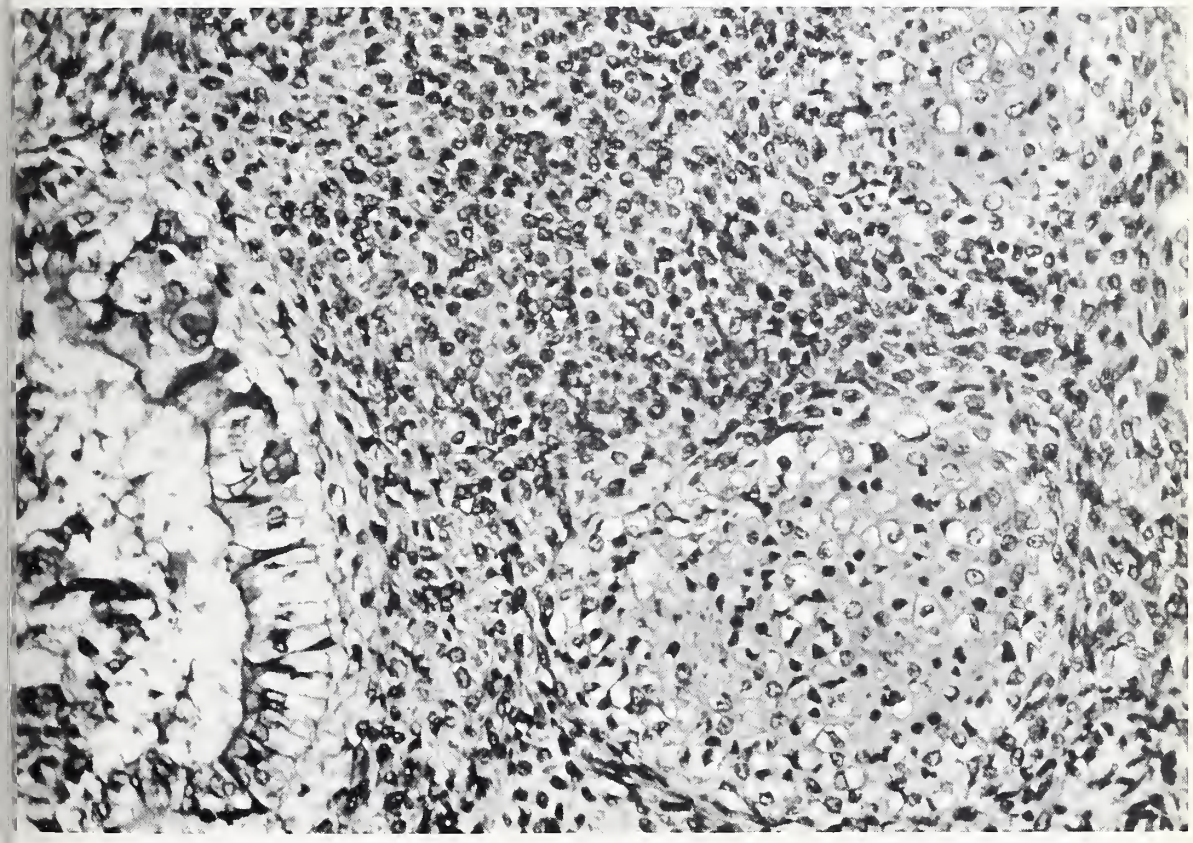

Fig. 62

Figure 63.* Liver cells and ductal epithelium in teratoma. Near center of photomicrograph a bile plug can be seen between liver cells. × 435. A. F. I. P. Acc. No. 141374.

Figure 64.* Neuroglial tissue in teratoma. Large island of neuroglia tissue contains several lined spaces suggestive of ependymal canals. × 125. A. F. I. P. Acc. No. 90042–1.

*From the Armed Forces Institute of Pathology.

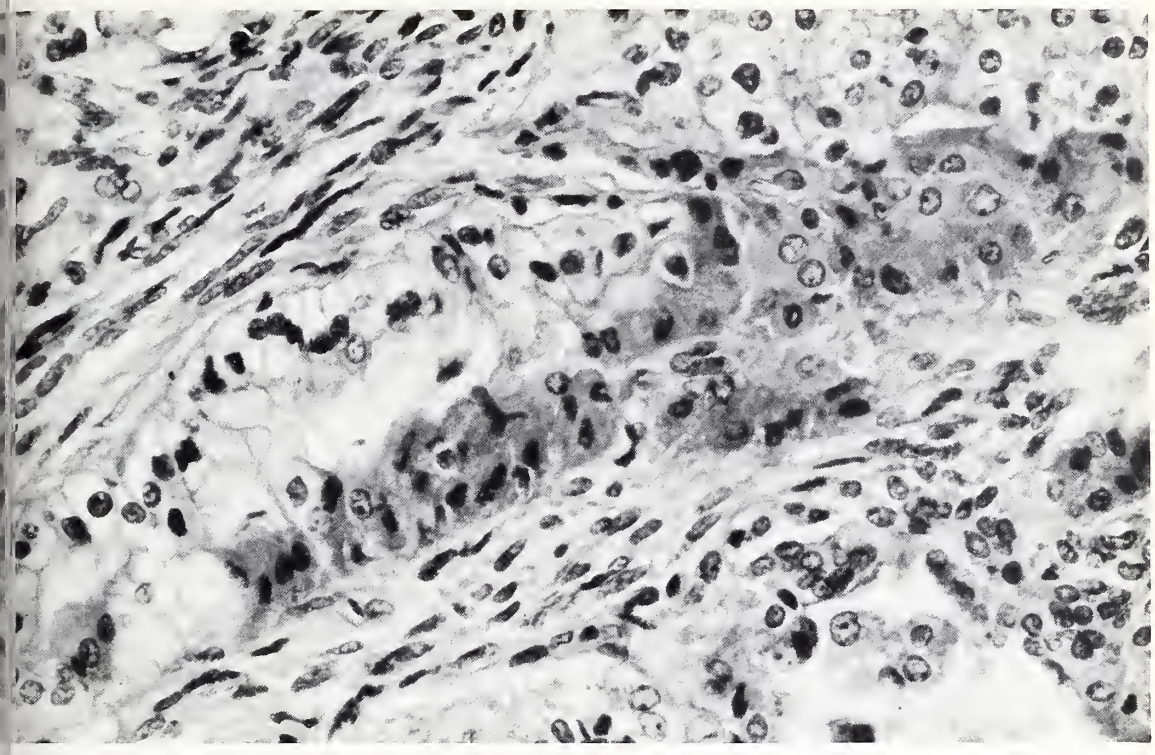

Fig. 63

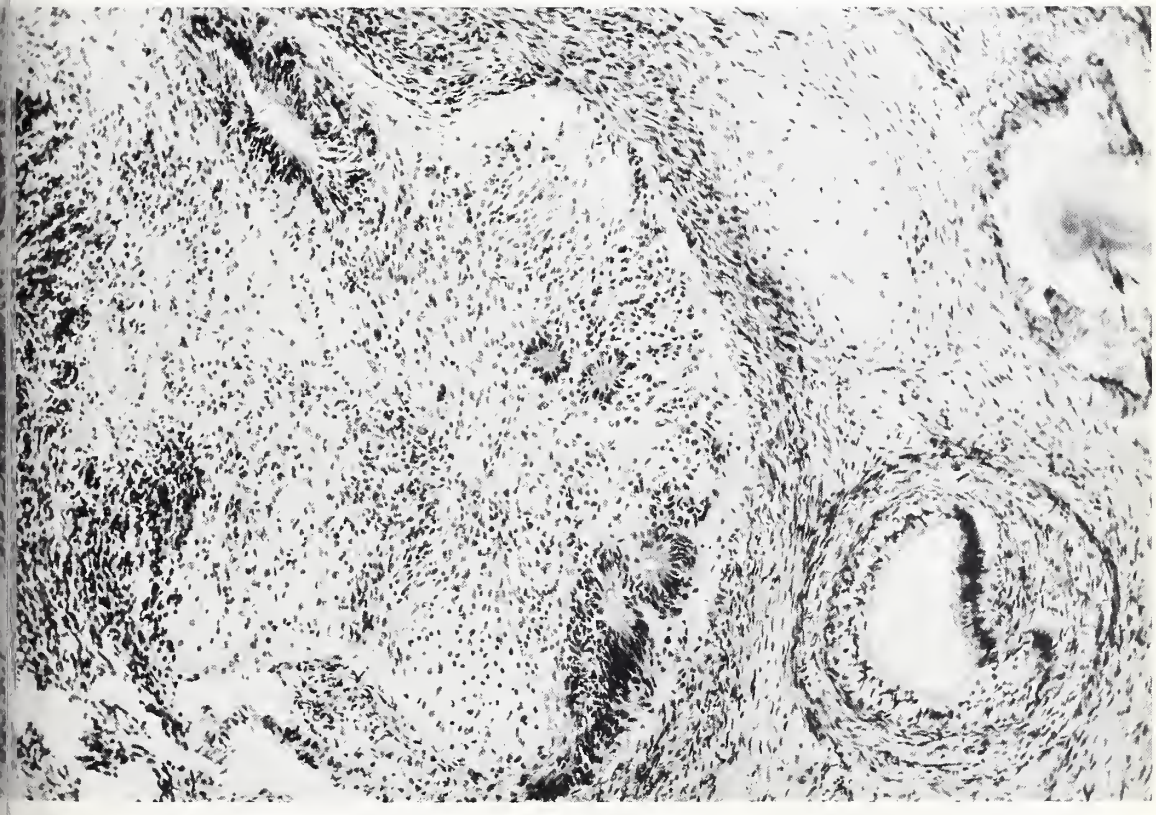

Fig. 64

Figure 65.* Structures resembling embryonic gut in teratoma. Organization of epithelium, submucosa, and smooth muscle are clearly illustrated. × 100. A. F. I. P. Acc. No. 190880.

Figure 66.* Fracture of bone spicule in teratoma. Well formed bone has been fractured with resultant giant cell response typical of ordinary fractures. × 155. A. F. I. P. Acc. No. 140035.

*From the Armed Forces Institute of Pathology.

Fig. 65

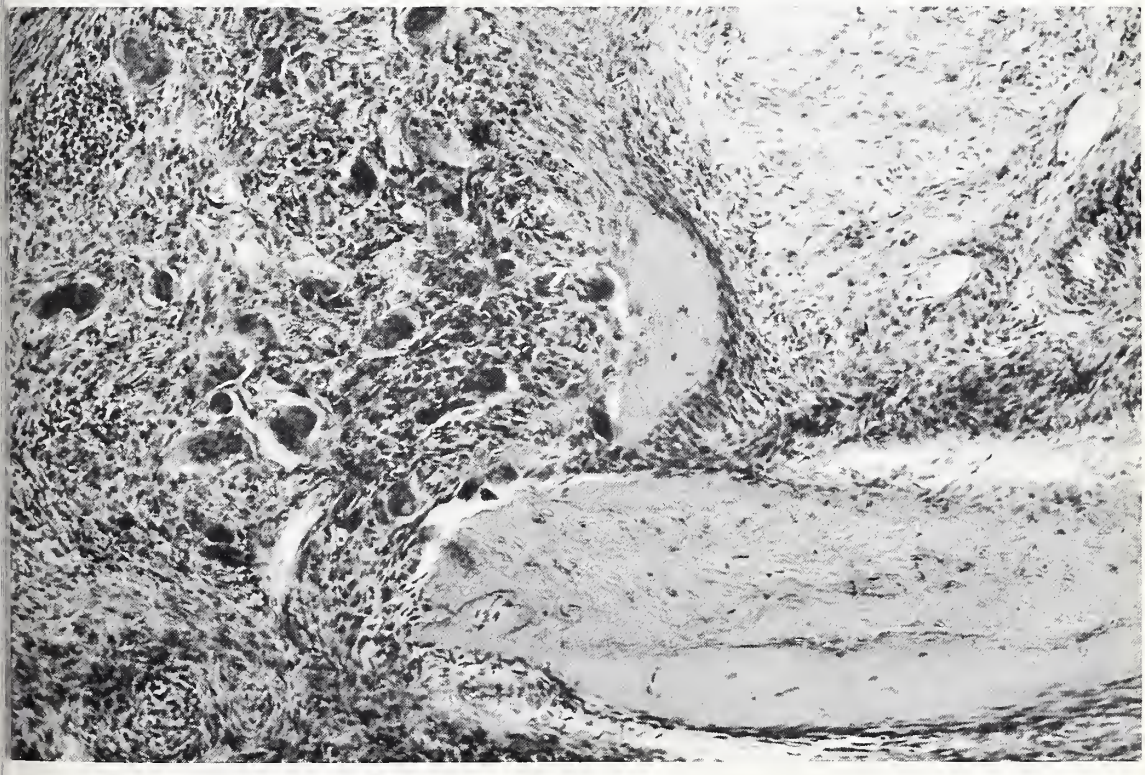

Fig. 66

Figure 67.* Melanin formation in teratoma. Melanin is occasionally found in teratomas and almost always in association with columnar epithelium. Epithelium and pigment suggest an optic structure. × 185. A. F. I. P. Acc. No. 90042–2.

Figure 68.* Striated muscle in stroma of teratoma. Occasional cross striations can be seen in the irregular muscle fibers. There is some orientation of the fibers around a cystic space, a part of which can be seen in lower left. × 185. A. F. I. P. Acc. No. 100993.

*From the Armed Forces Institute of Pathology.

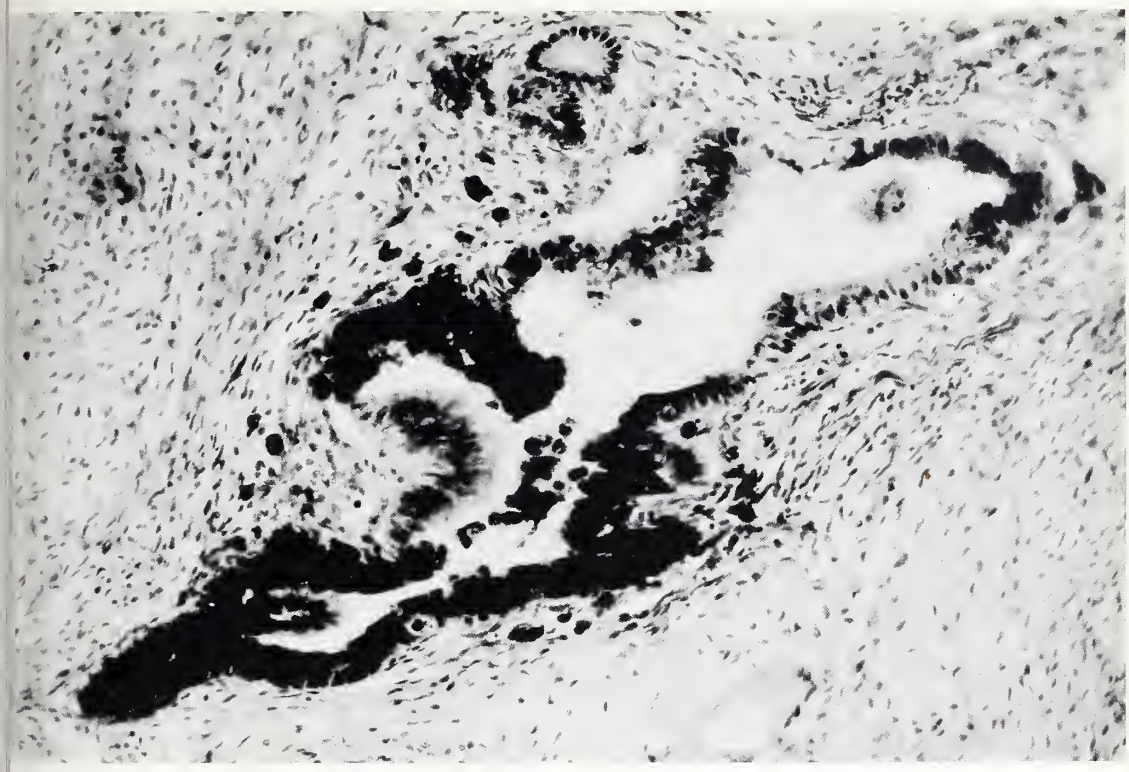

Fig. 67

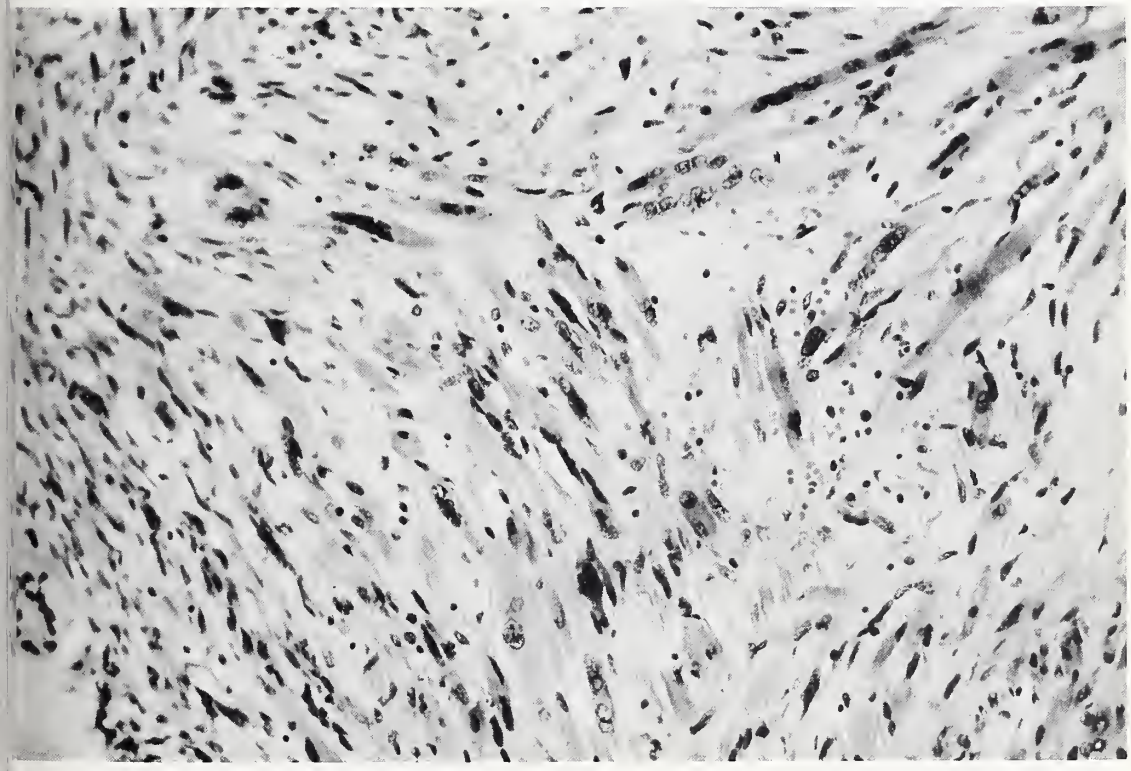

Fig. 68

carcinoma could have occurred while the primary tumor was still an embryonal carcinoma, before its differentiation into teratoma.

The reaction of interstitial cells was correlated with prognosis: those cases with hyperplasia of interstitial cells had a 71 percent 2–year mortality, and those with normal interstitial cells, a 21 percent 2–year mortality.

Tumor Group IV—Teratoma with Either Embryonal Carcinoma or Choriocarcinoma or Both and with or without Seminoma

DEFINITION. The essential elements in Group IV are teratoma plus either embryonal carcinoma or choriocarcinoma. The presence of teratoid differentiation in tumors containing embryonal carcinoma and choriocarcinoma is associated with a reduction in the malignancy displayed by the latter when no teratoid differentiation is present.

INCIDENCE. Group IV tumors made up 32 percent of germinal tumors found in the army series but would be expected to make up 19 percent in the total population. These tumors have their highest incidence in the third decade, thus accounting for their frequency in the army series.

CLINICAL COURSE AND TREATMENT. Chief complaints in patients with Group IV tumors were gradual testicular enlargement (77 percent) and pain (57 percent). About one third had symptoms more than six months before seeking medical aid. Nearly one fifth of cases had metastases at time of first examination. There was little evidence of a relationship between pain or delay before treatment and prognosis in this group.

Urinary gonadotropin tests were positive in 23 percent of patients tested preoperatively and in 15 percent of those tested after surgery.

The treatment in 96 percent of these cases was surgery followed by radiation and in one percent surgery alone. In the 97 percent of patients treated surgically, the mortality within the first two years after operation was 48 percent and within the first five years was 52 percent (table II). Peak mortality was in the first two years with no deaths noted after four years (table III).

Clinical features of prognostic aid were positive gonadotropin tests associated with a 69 percent 2–year mortality and negative gonadotropin with a 47 percent; presence of metastases at first examination was associated with an 84 percent 2–year mortality and absence of metastases with a 41 percent 2–year mortality.

GROSS. Group IV tumors have a mean volume of 85 cc. with considerable variation: 25 percent are less than 20 cc. and 30 percent are greater than 100 cc. The tumor replaces most or all of the testis and irregularly distends the capsule. Twelve percent showed extratesticular extension of tumor. Of patients with extratesticular extension, 70 percent died within two years, and of those without exension, only 43 percent died within two years.

On section the tumor combines the gross appearances of Groups II, III,

and V with cystic areas of teratoma and hemorrhagic, infiltrating embryonal carcinoma and choriocarcinoma.

Distribution of metastases as determined from 93 autopsies was as follows: periaortic and iliac lymph nodes, 92 percent; each lung, about 80 percent; liver, 70 percent; brain, 40 percent; and pleura, 33 percent.

MICROSCOPIC. The histologic characteristics of the various elements comprising this tumor group are described elsewhere: seminoma under Group I, embryonal carcinoma under Group II, teratoma under Group III, and choriocarcinoma under Group V.

Microscopic structure of metastases in 74 cases was as follows: embryonal carcinoma in 80 percent, teratoma in 42 percent, and choriocarcinoma in 30 percent. However, in all cases with metastases where there were elements of choriocarcinoma in the primary there were choriocarcinomatous metastases.

Those patients having hyperplasia of interstitial cells had a 69 percent 2–year mortality, and those with normal interstitial cells, a 47 percent mortality.

Tumor Group V—Choriocarcinoma, Pure or with either Seminoma or Embryonal Carcinoma or Both

SYNONYMS AND RELATED TERMS: Carcinoma syncytiale; chorioma (ectodermale); chorio(n) epithelioma (malignum); chorio(n) carcinoma; chorionic carcinoma; choriosarcoma; epithelioma chorio-epidermale (Pick); syncytial carcinoma; syncytioma malignum; trophoblastoma.

DEFINITION. The essential element in Group V tumors is choriocarcinoma, a highly malignant tumor composed of cytotrophoblast and syncytial trophoblast partially in villus-like arrangement.

INCIDENCE. Only one percent of germinal tumors fall into this category.

CLINICAL COURSE. Pain and slight swelling of the testis were the most frequent symptoms in army patients. Metastases were frequently present at time of diagnosis. These tumors ran a uniformly fatal course, with death usually occurring within two years from time of diagnosis. There was little evidence of any response to radiation therapy.

GROSS. Group V tumors are usually small, often replacing only part of the testis. From the external surface the testis may appear normal or slightly enlarged. On section the tumor is largely necrotic and hemorrhagic. Viable tumor tissue can be seen around the periphery of the necrotic, hemorrhagic regions.

These tumors metastasize widely. On the basis of seven autopsies, the distribution of metastases was: periaortic and iliac nodes, 100 percent; each lung, 100 percent; liver, 86 percent; intestine, 71 percent; and spleen, adrenals, and brain, 56 percent.

MICROSCOPIC. Choriocarcinoma of the testis is histologically very similar to its homologue in the uterus. It is made up of two elements: (1) fairly uniform, closely packed cytotrophoblast, having clear cytoplasm, distinct

Figure 69.* Well differentiated choriocarcinoma. Cytotrophoblast is made up of characteristic uniform cells with clear cytoplasm, and forms villus-like masses, the surfaces of which are covered by syncytial trophoblast with dark eosinophilic cytoplasm. × 125. A. F. I. P. Acc. No. 194644–1.

Figure 70.* High power view of choriocarcinoma seen in figure 69. Detail of cytotrophoblasts and syncytiotrophoblasts is evident. × 235. A. F. I. P. Acc. No. 194644–2.

*From the Armed Forces Institute of Pathology.

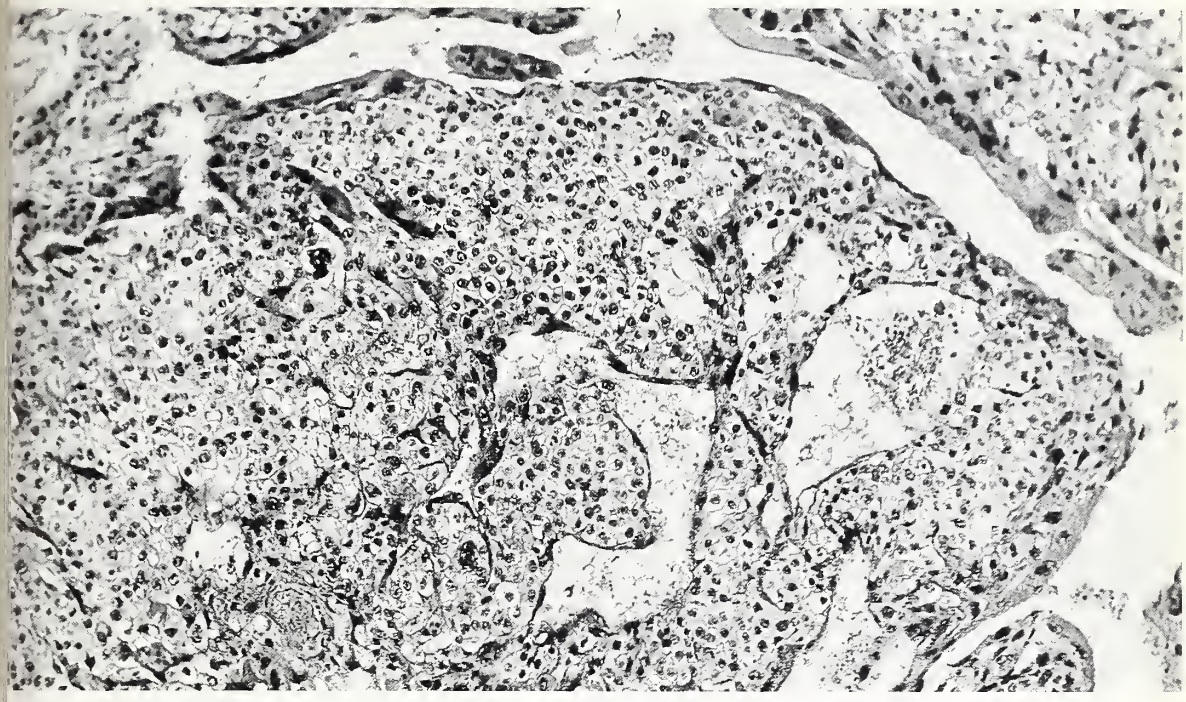

Fig. 69

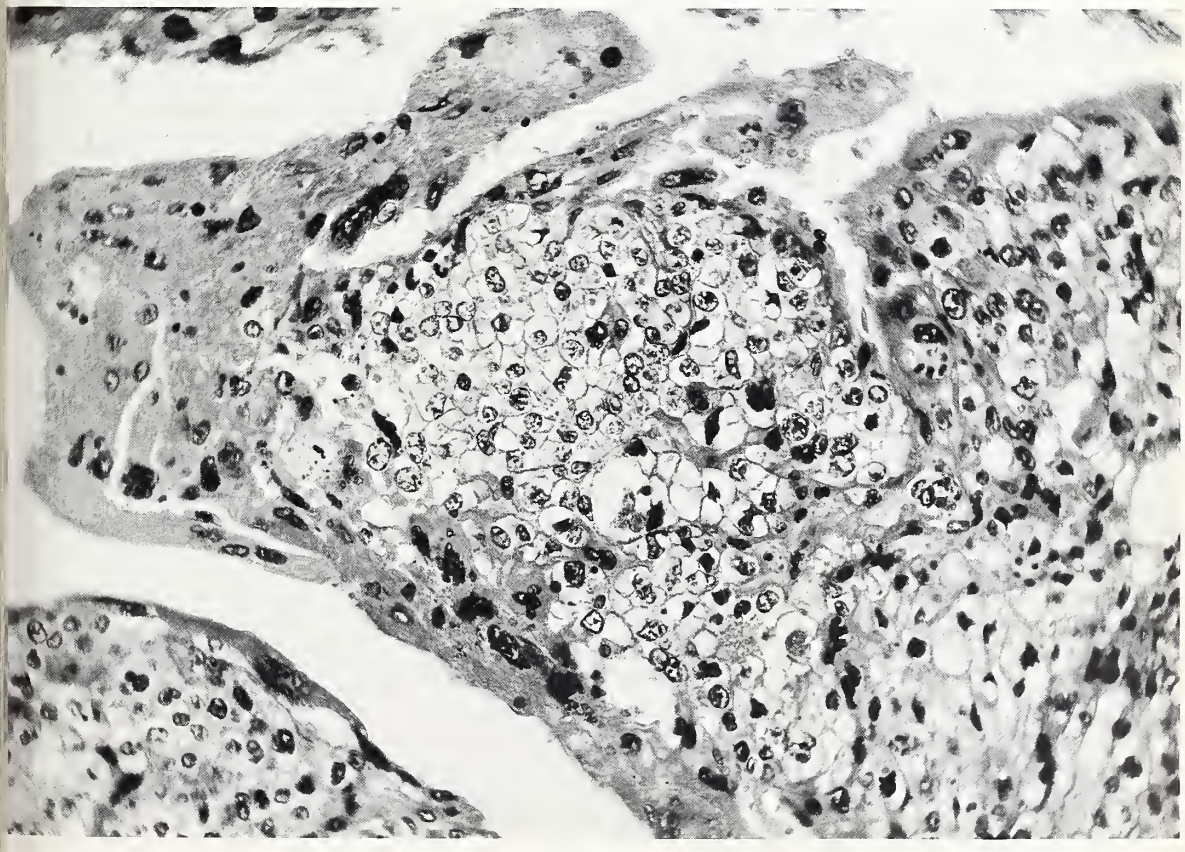

Fig. 70

cell borders, and uniform, moderate-sized nuclei; and (2) typical syncytial trophoblast—large, multinucleate cells with deep eosinophilic or amphophilic vacuolated cytoplasm and numerous irregular, dark-staining nuclei. There is always some formation of villus-like structures, with a core of cytotrophoblast and stroma covered by an irregular layer of syncytial cells (figs. 69–71).

When embryonal carcinoma was found in these Group V tumors, it was intimately associated with the choriocarcinoma and usually showed intermediate trophoblastic differentiation. Seminomatous components were, on the other hand, usually distinct from the choriocarcinoma.

The extremely malignant nature of the choriocarcinoma was demonstrated by the fact that not only did all Group V tumors metastasize as choriocarcinoma but all the autopsied Group IV tumor cases with choriocarcinomatous elements in the primary tumor also metastasized as choriocarcinoma.

Extragenital choriocarcinoma associated with a scar in the testis. Rarely, extensive metastases of a choriocarcinoma are observed at autopsy with only a pigmented scar in the testis. It has been postulated by some that the scar represents spontaneous regression of a primary choriocarcinoma. In other rare instances there is a small, clinically undetected teratoma in the testis. Hence, a choriocarcinoma should not be accepted as of extragonadal origin without careful gross and histologic study of the testes.

Reference

Lewis, L. G. Testis tumors. Advances in Surgery, 2: 419–494, 1949.

NONGERMINAL TUMORS

Of the numerous kinds of nongerminal tumors—interstitial cell tumors, androblastomas, fibromas, angiomas, neurofibromas, adenomatoid tumors, sarcomas, and adenocarcinomas of the rete—only two will be taken up in detail. These are interstitial cell tumors and androblastomas, both true tumors of the gonad. Sarcomas, which in most instances are really a one-sided development of a teratoma, are illustrated (figs. 72–76) but not discussed. The tumors arising in stroma, vessels, and nerves of the testis are similar to their counterparts found elsewhere and need no special consideration. Adenomatoid tumors, which are more frequently found in the epididymis than in the testis, and fibromas, which arise in the testicular tunics, are discussed in the section on tumors of the testicular appendages. Adenocarcinomas of the rete are too rare (two reports in the literature) to permit any discussion, but figures from one of the two reported cases are presented (figs. 77, 78). It is worthy of note that in our series we found no Sertoli cell tumors, indicating that there may be no human homologue of the Sertoli cell tumors seen so frequently in dogs.

Interstitial Cell Tumors

SYNONYMS AND RELATED TERMS: Gynandroblastoma; interstitioma; Leydig cell tumor.

DEFINITION. Usually benign tumors of Leydig cells which may be associated with hypersecretion of male sex hormones.

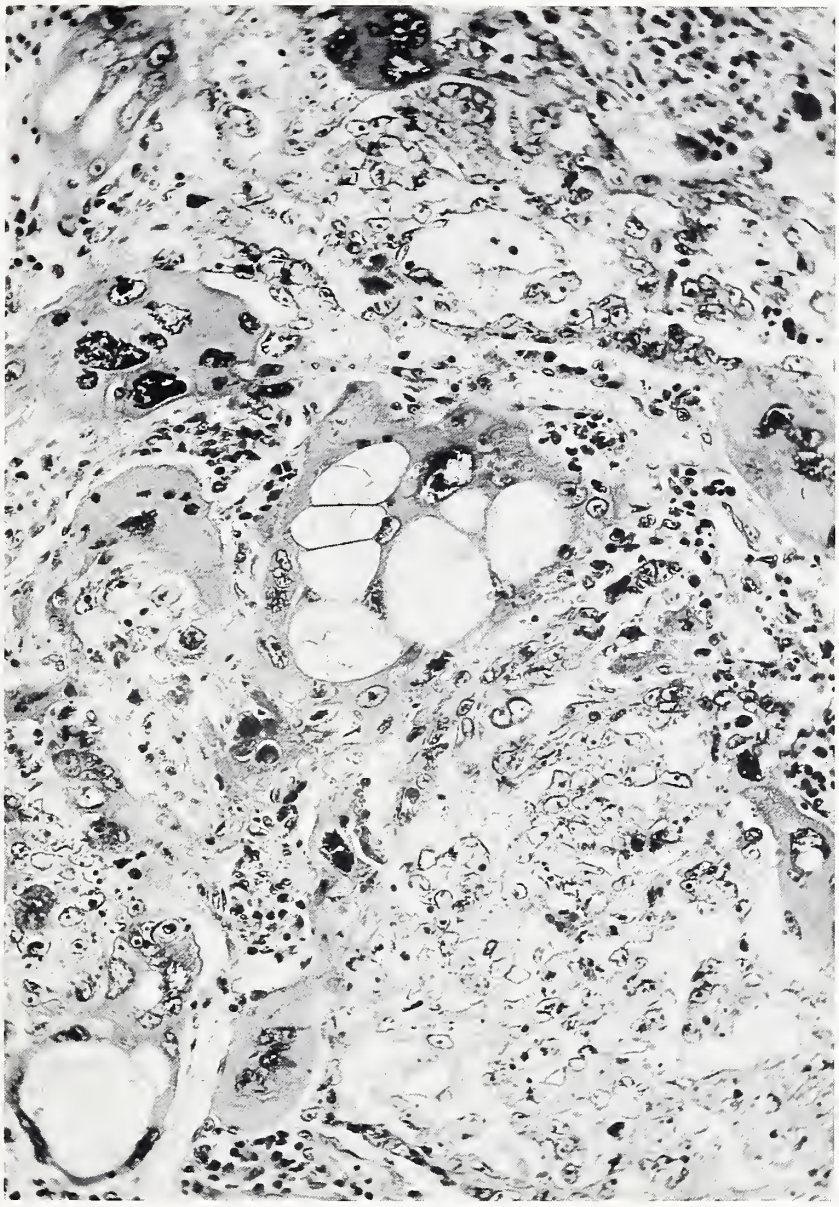

Figure 71. Atypical choriocarcinoma. Both cytotrophoblast and syncytiotrophoblast are present, but no villus formation is seen. Many of the large spaces in the syncytial cells are true vascular spaces. × 210. (From the Armed Forces Institute of Pathology.) A. F. I. P. Acc. No. 93056.

Figure 72.* Rhabdomyosarcoma, probably a one-sided development of a teratoma. Irregular, elongated, multinucleated giant cells are characteristic. Cross striations are not visible at this power. × 320. A. F. I. P. Acc. No. 84937.

Figure 73.* Cross striations of muscle fibers in a teratoma. Foci of striated muscle proliferation are not infrequently seen in the connective tissue of teratoma. × 810. A. F. I. P. Acc. No. 131087.

*From the Armed Forces Institute of Pathology.

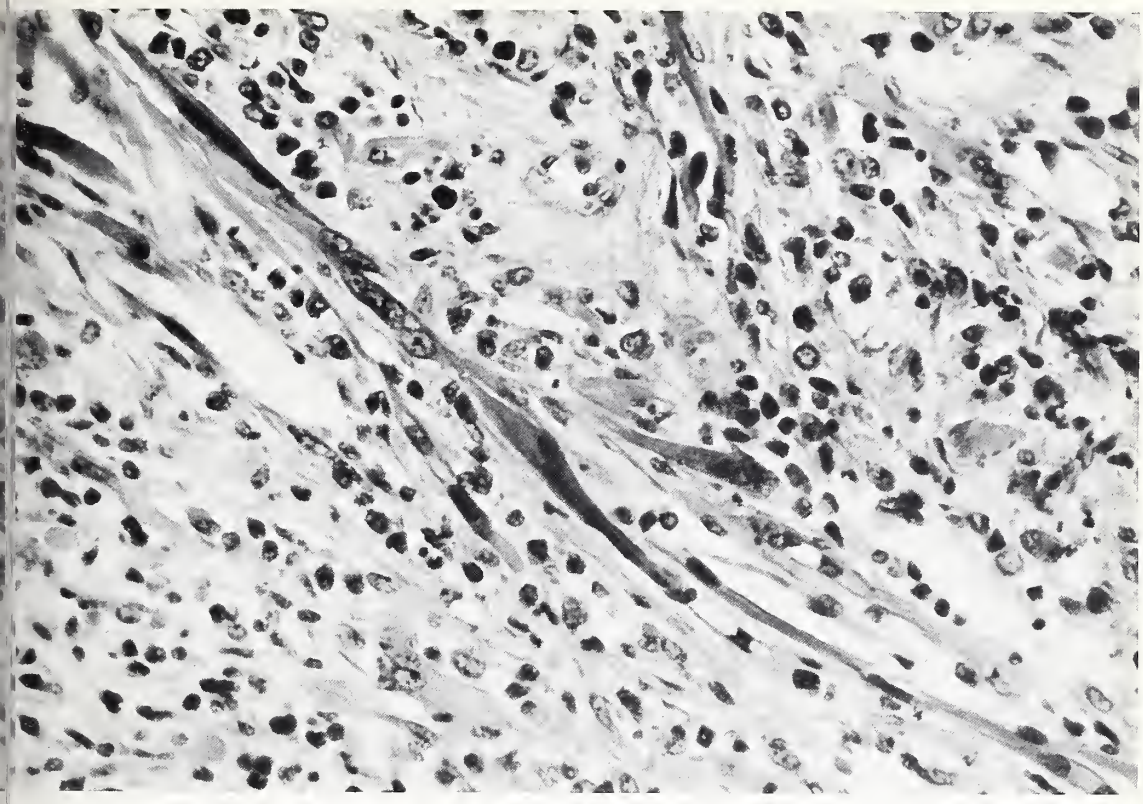

Fig. 72

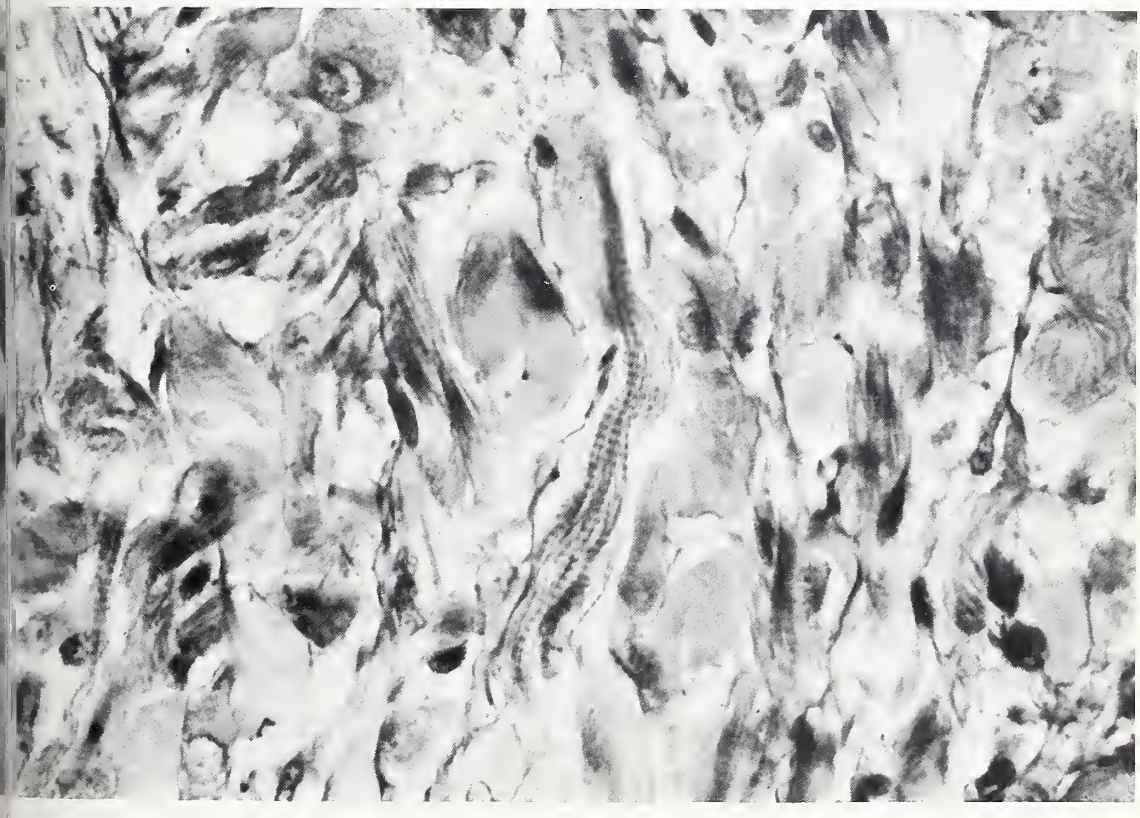

Fig. 73

Figure 74.* Myxosarcomatous field in teratoma. Fibrillogranular precipitation of mucoid ground substance is characteristic. × 355. A F. I. P. Acc. No. 175159.

Figure 75.* Undifferentiated sarcoma of testis. This tumor was the only pure sarcoma in the army series. Absence of any specific differentiation of tumor cells, as evidenced by collagen, mucoid, or cartilage production, indicates immaturity of these malignant mesenchymal cells. × 355. A. F. I. P. Acc. No. 76024.

*From the Armed Forces Institute of Pathology.

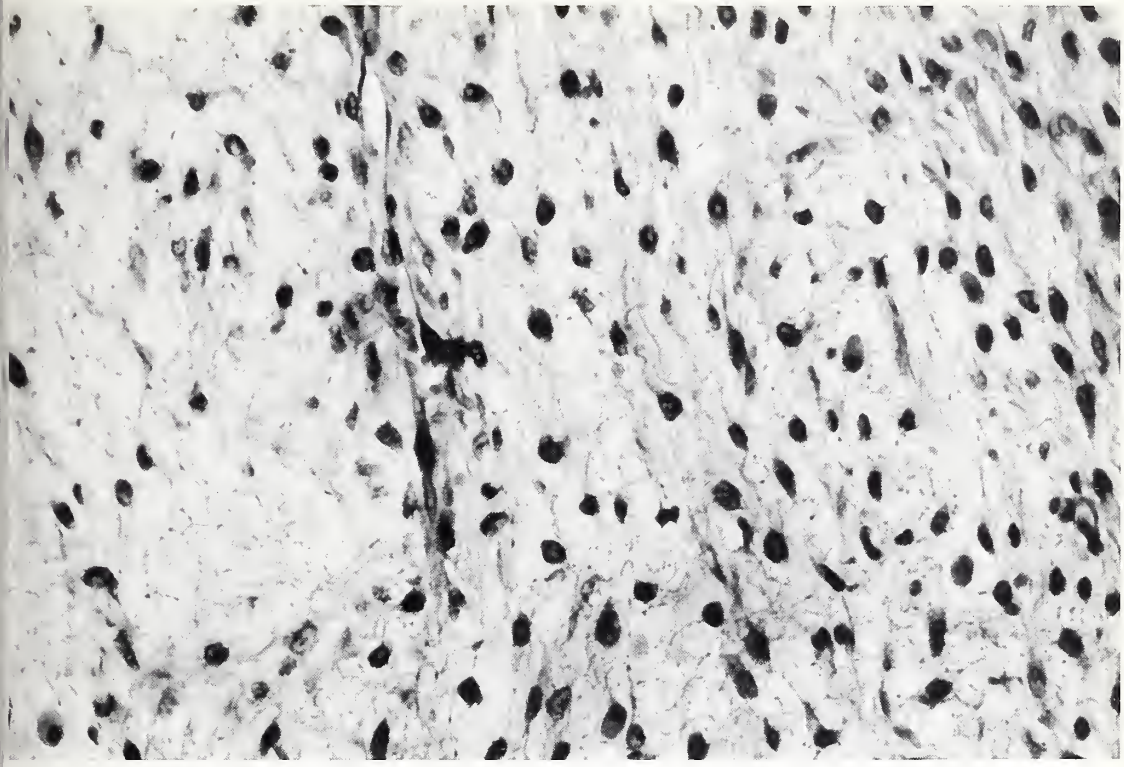

Fig. 74

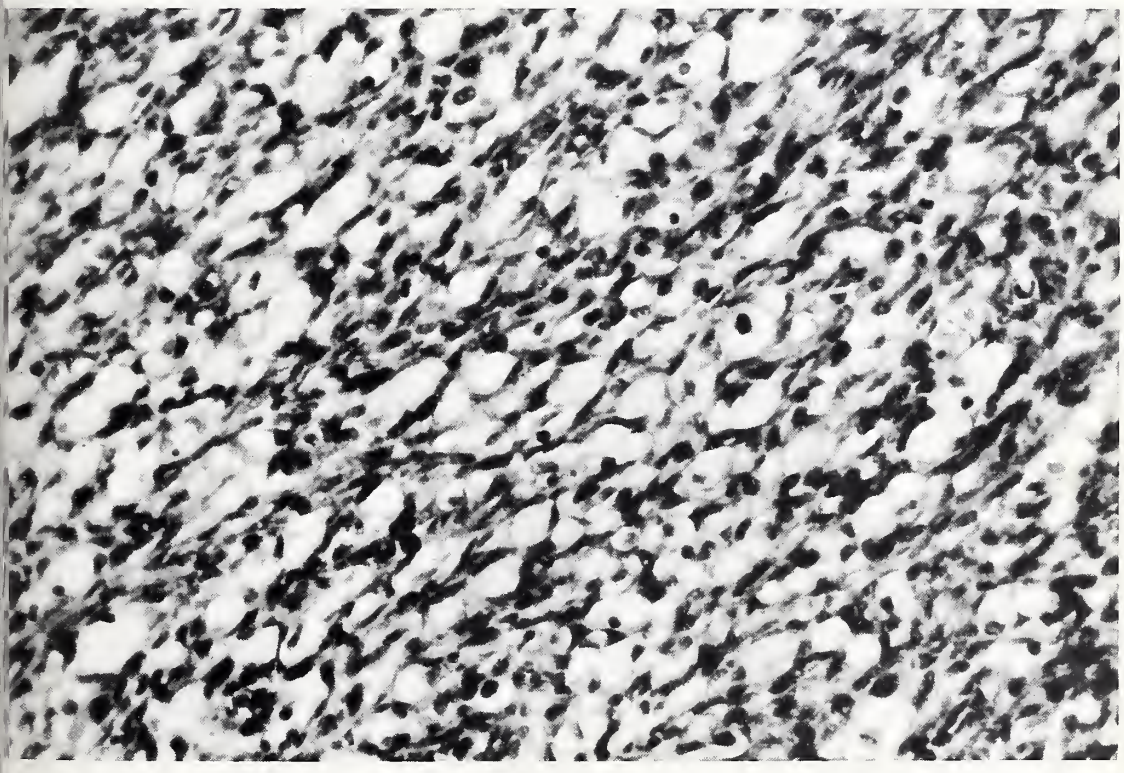

Fig. 75

NATURAL HISTORY. Interstitial cell tumors are extremely rare. A recent review lists a total of 37 reported cases in the literature: 27 adults and 10 children. In the army series interstitial cell tumors made up 1.2 percent of all testicular tumors. They may occur at almost any age, with reported extremes of 4 and 82 years; but their incidence definitely declines after 50 years.

In children, the first signs and symptoms of interstitial cell tumor are usually associated with precocious sexual development; local signs of tumor appear later. All children with interstitial cell tumors have shown macrogenitosomia, pubic hair, and deep voice. Removal of tumor caused complete regression of symptoms and signs in one third of patients, partial regression in one third, and no change in the rest.

In adults, gradual testicular enlargement with or without pain is usually the first indication of an interstitial cell tumor, while signs and symptoms resulting from hormonal activity are unusual. This does not mean that in adults these tumors secrete no hormone, but rather that an excess of androgen is not associated with any constant bodily changes in the adult male. An output of androgenic hormones 50 times normal was recorded in one patient with an interstitial cell tumor.

In about 1 of every 10 patients with interstitial cell tumor there is associated gynecomastia (fig. 79). The presence of a feminizing trait in a patient with an androgen-secreting tumor seems paradoxical. However, at least two possible explanations exist. First, an excess of androgen per se may stimulate the breasts, as occurs following prolonged testosterone therapy in hypogonad males. Second, the possibility that an excess formation of estrogen may coexist with the excess formation of androgen in patients with interstitial cell tumors is suggested by the hormone assays of Masson in a single case.

Interstitial cell tumors are most often benign. Only five of the 37 reported tumors have been malignant. One tumor metastasized and killed after nine years, which would indicate the necessity of long follow-up periods for these patients. However, none of the 12 interstitial cell tumors in the army series, followed from three to 15 years, gave evidence of metastases or recurrence.

GROSS. Interstitial cell tumors vary from a few to more than 100 cc. at time of detection. They are usually roughly spherical, lobulated, and discrete, compressing a surrounding rim of testicular parenchyma. Cut surface varies from yellow to rusty brown and is homogeneous, firm, and bulging, without necrosis or hemorrhage. Occasionally multiple nodules of tumor are found within the testis.

MICROSCOPIC. Usually interstitial cell tumors are composed of relatively uniform, polyhedral, closely packed cells with eosinophilic granular cytoplasm containing lipoid vacuoles, brown pigment, and sometimes crystalloids (three of our 12 cases), and with round, slightly eccentric nuclei (fig. 80). Occasionally

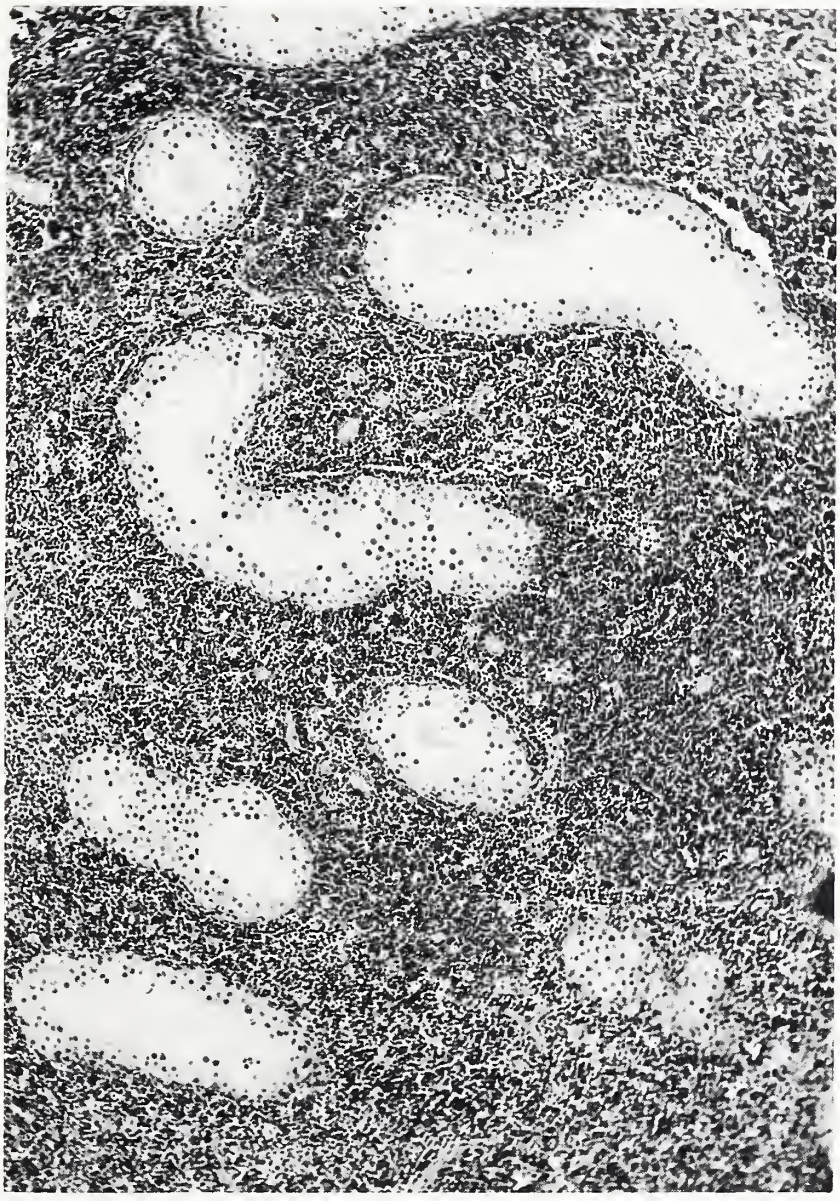

Figure 76. Secondary involvement of testis by lymphosarcoma. Although a few instances of primary lymphosarcoma of the testis have been reported, all have been associated with generalized disease. The occurrence of primary testicular lymphoma is at least questionable. Filling of interstitial tissue by uniform tumor infiltrate with separation but preservation of tubules is characteristic. × 115. (From the Armed Forces Institute of Pathology.) A. F. I. P. Acc. No. 138909.

Figure 77.* Papillary adenocarcinoma of rete. Rete passages are partially filled with papillary tumor growth. Almost all of rete epithelium is involved and invasion of connective tissue stroma is evident. × 75. A. F. I. P. Acc. No. 173676–1.

Figure 78.* Cell detail of carcinoma of rete seen in figure 77. Papillary glandular nature of tumor is evident. × 355. A. F. I. P. Acc. No. 173676–3.

*Case contributed to the Armed Forces Institute of Pathology by Dr. J. D. Feek and Dr. W. C. Hunter, Portland, Oregon.

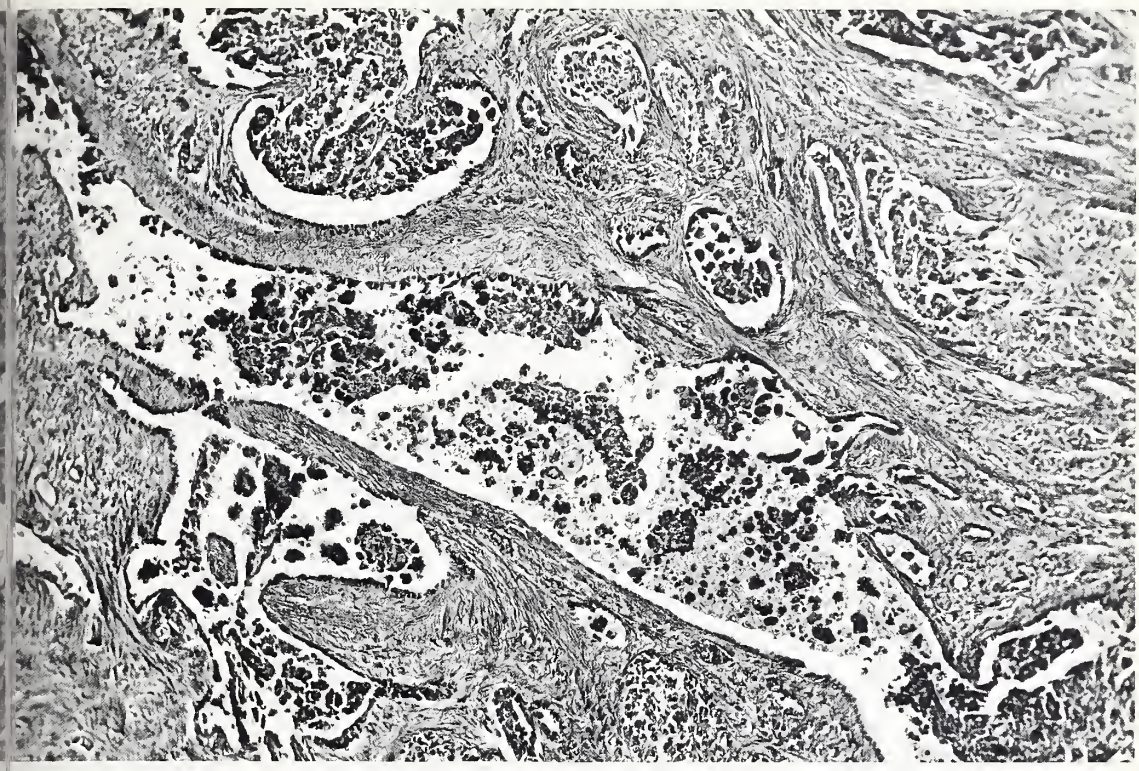

Fig. 77

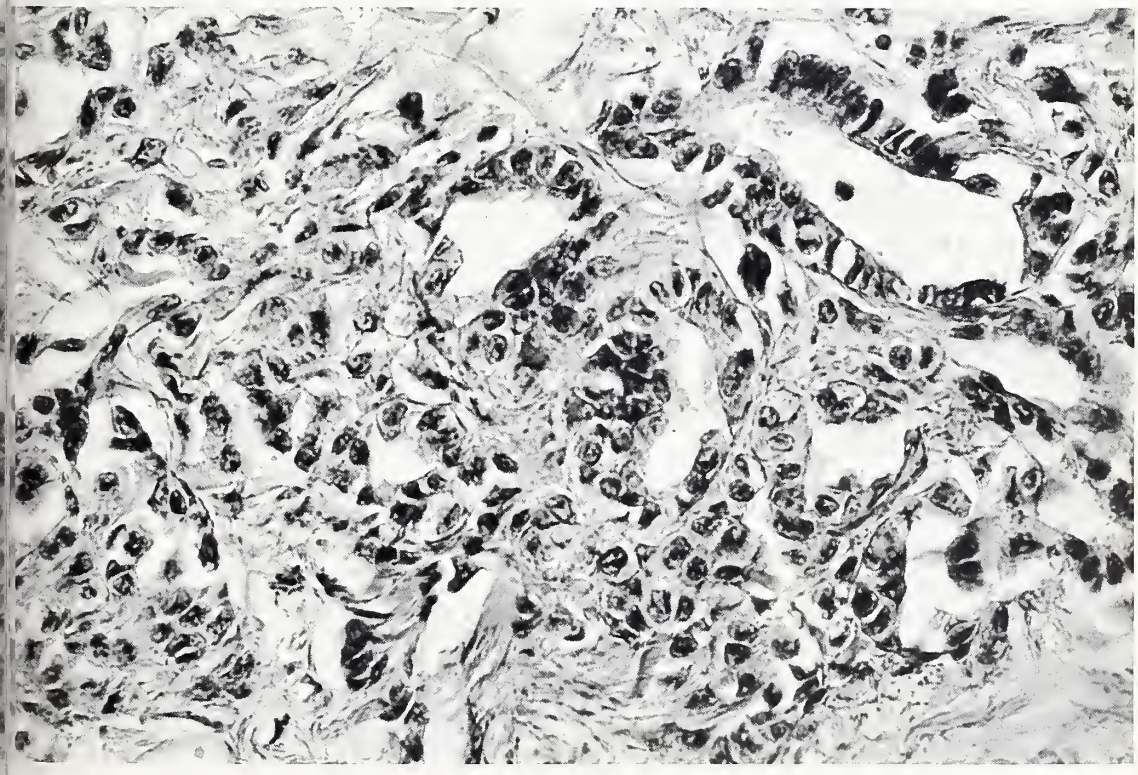

Fig. 78

there is considerable anaplasia which, however, is not necessarily associated with a malignant course (fig. 81). Rarely, degenerative changes in the tumor leave relatively few interstitial cells in an edematous acellular stroma.

There is no capsule around these tumors, although they are usually clearly demarcated and compress the surrounding testis. The number of interstitial cells in the remaining testicular parenchyma may be decreased, normal, or diffusely increased.

DIFFERENTIAL DIAGNOSIS. Marked hyperplasia of interstitial cells can bear some resemblance to tumors. However, the process is usually diffuse and forms no discrete nodules within the testis (fig. 82). Microscopically, the hyperplastic interstitial cells fill and distend the pre-existing intertubular spaces without destroying or displacing the tubules. In advanced examples, the widely separated tubules seem regularly placed in a sea of interstitial cells.

Aberrant adrenal cortical rests associated with testis or spermatic cord may closely resemble interstitial cells, and tumors derived from these two sources might well be impossible to differentiate (fig. 83). These adrenal rests are seen occasionally along the spermatic cord or even in the epididymis and testicular rete. However, there were none in the testicular parenchyma proper in any of the army series. They are easily recognized when they retain a fascicular architecture resembling that of the normal adrenal cortex.

ANIMAL AND EXPERIMENTAL. Spontaneously occurring interstitial cell tumors have been observed in animals, and such tumors have also been produced in animals by hormonal stimulation. Interstitial cell tumors occasionally occur spontaneously in horses and birds and are common in old dogs. In dogs interstitial cell tumors are the most common testicular tumor and are almost always benign.

Interstitial cell tumors have been produced in male mice by prolonged administration of estrogens. In rats, interstitial cell tumors have been produced in castrates of either sex by intrasplenic grafts of immature testicular tissue. These two observations indicate the relationship of hormonal imbalance and the genesis of interstitial cell tumors.

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Figure 79. Gynecomastia in fatal case of tumor of the testis. Note loose, edematous connective tissue within the lobules and hyperplasia of duct epithelium. No acini are found in this condition. × 100. (From the Armed Forces Institute of Pathology.) A. F. I. P. Acc. No. 106546.

Figure 80.* Interstitial cell tumor. Note granularity and vacuolation of cytoplasm, seen best in well preserved material. Two crystalloids are indicated by arrows. × 655. A. F. I. P. Acc. No. 101379.

Figure 81.* Interstitial cell tumor showing moderate degree of anaplasia. There is no evidence that anaplasia can be correlated with malignant or benign course of tumor. × 400. A. F. I. P. Acc. No. 93145.

*From the Armed Forces Institute of Pathology.

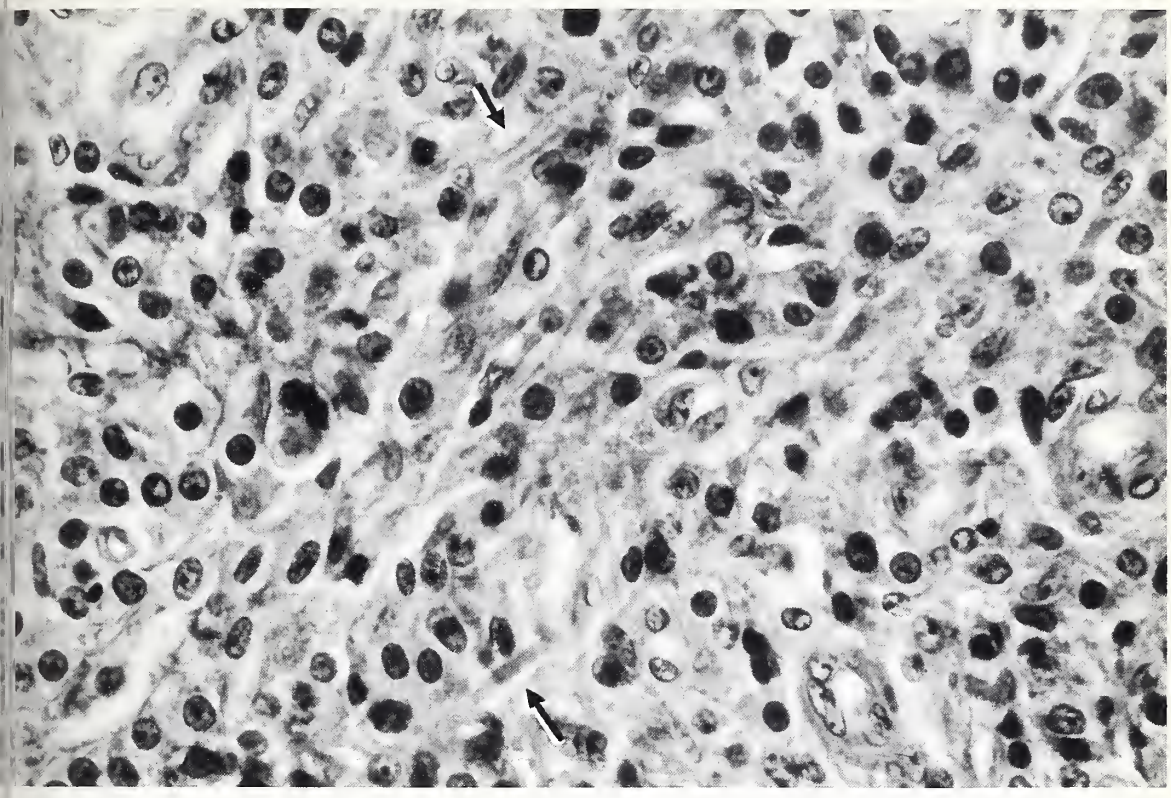

Fig. 80

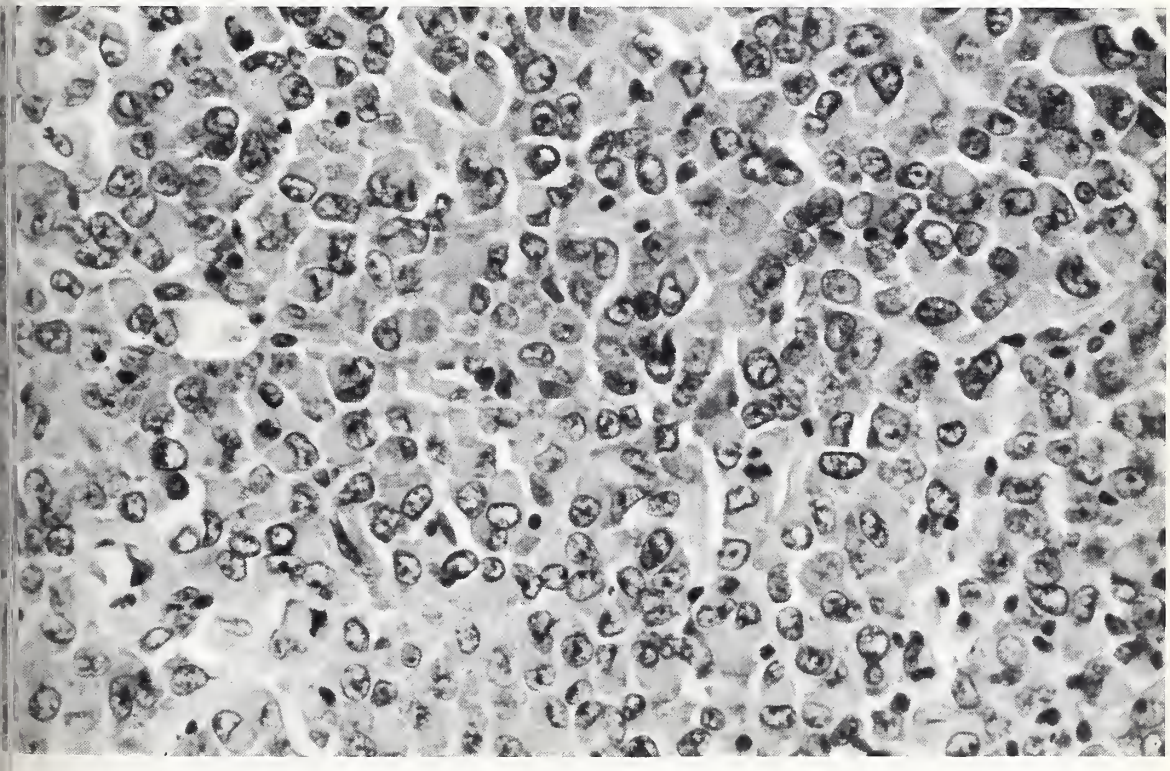

Fig. 81

Figure 82.* Hyperplasia of interstitial cells. Stroma is uniformly distended by closely packed interstitial cells. The tubular atrophy evident here may be, but is not always, associated with hyperplasia of interstitial cells. × 125. A. F. I. P. Acc. No. 106389.

Figure 83.* Extratesticular interstitial cells in spermatic cord. Masses of Leydig cells such as this are frequently incidental findings along nerves and vessels of spermatic cord. Absence of fascicular arrangement of cells and presence of crystalloids aid in differentiation from adrenal cortical rests. × 185. A. F. I. P. Acc. No. 132104.

*From the Armed Forces Institute of Pathology.

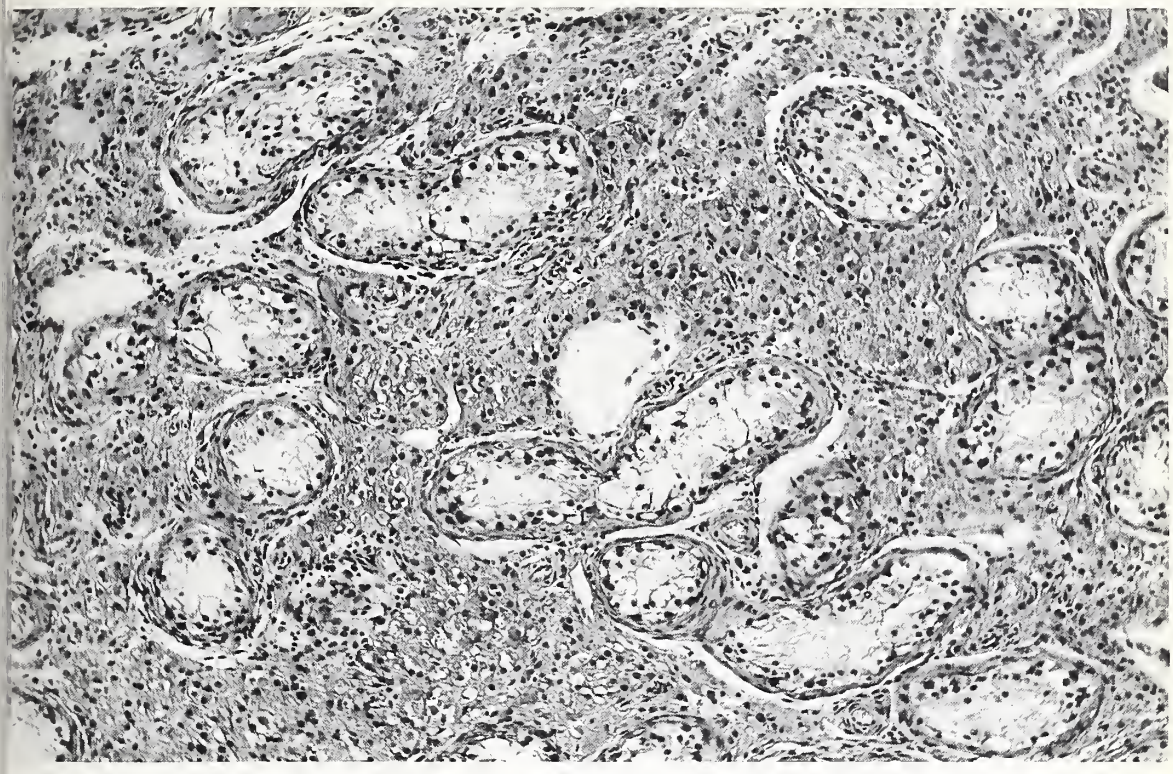

Fig. 82

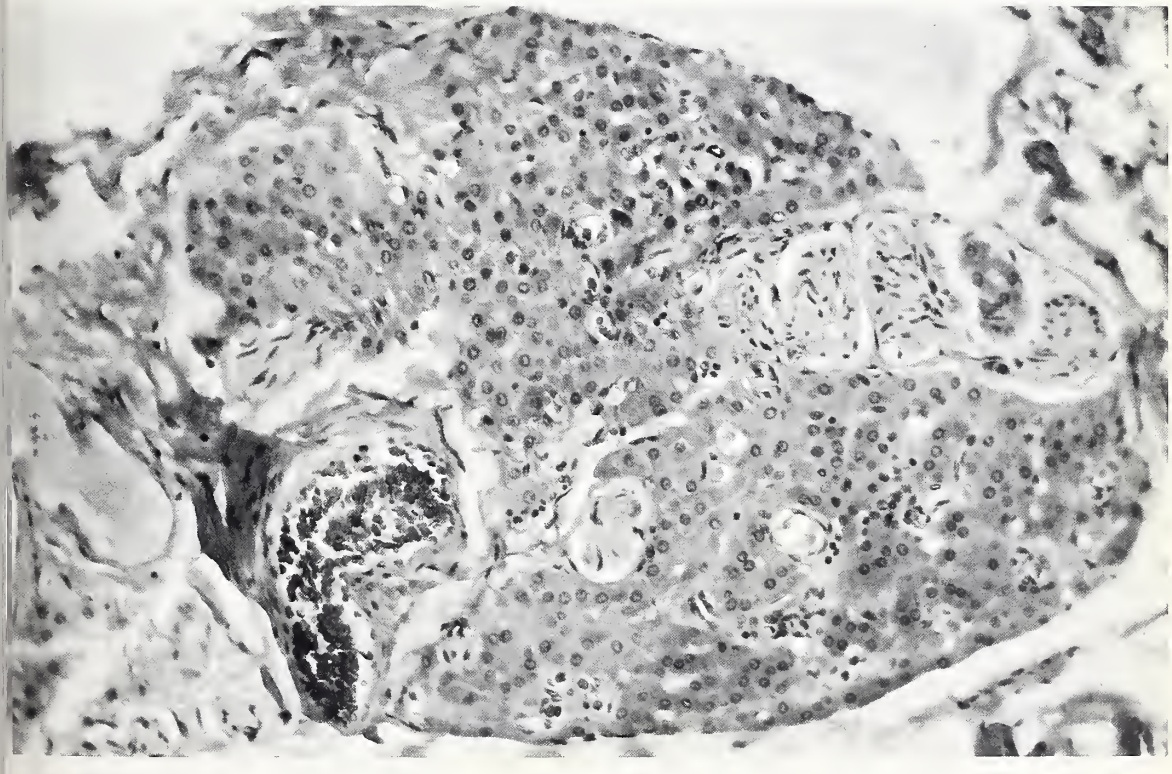

Fig. 83

Twombly, G. H., Meisel, D., and Stout, A. P. Leydig-cell tumors induced experimentally in the rat. Cancer, 2: 884–892, 1949.

Androblastomas

SYNONYMS AND RELATED TERMS: Testicular adenoma (Pick). (In the female, arrhenoblastoma; see Fascicle 33, "Tumors of the Female Sex Organs.")

DEFINITION. Androblastomas are testicular homologues of ovarian arrhenoblastomas. They are rare tumors resembling fetal testes and may be associated with feminizing characteristics in the male.

NATURAL HISTORY. Teilum first recognized androblastomas and has reported three cases, one of which was associated with gynecomastia. According to the army studies, these tumors make up 0.4 percent of testicular tumors.

Like the arrhenoblastomas, the androblastomas are composed histologically of either epithelial tubules or diffuse stroma or both. Depending upon the proportions of these two components, there is the following classification of androblastomas: (1) tubular, (2) mixed, and (3) diffuse stromal. The tubular form has long been recognized in both ovary and testis as the testicular tubular adenoma (figs. 84, 85). The mixed and diffuse stromal types in the ovary were described by Meyer but have only recently been reported in the testis by Teilum (figs. 86, 87).

HISTOGENESIS. Because of the histologic resemblance of both androblastoma and arrhenoblastoma to the immature testis, plus the androgenic effect of the arrhenoblastomas, it has been postulated that they arise in either ovary or testis from immature testicular remnants retaining male potentialities.

CLINICAL COURSE. The most intriguing aspect of these tumors is their hormonal influence on the host. The masculinizing effects of arrhenoblastomas, especially the mixed and diffuse forms, are well recognized. It may at first appear inconsistent that the same tumor can be associated with feminizing traits in the male. However, Teilum's postulation that the tubular epithelial elements in these growths are analogous to Sertoli cells and are potentially capable of estrogen formation, while the stromal tissue is related to Leydig cells and is therefore potentially androgenic, might account for this apparent contradiction. In support of this view, it should be noted that the arrhenoblastomas with androgenic activity have a considerable stromal component, while the one androblastoma associated with feminization was in great part composed of tubular epithelial structures.

None of the reported tubular adenomas, the androblastomas of Teilum, or the four androblastomas in our series have been malignant. However, the possibility exists of malignant variants of androblastoma, as indicated by the not infrequent occurrence of malignant arrhenoblastomas.

Data on six mixed and diffuse androblastomas (three reported by Teilum and three in our series) show them to occur at almost any age, with ex-

tremes of four and 52 years, usually in scrotal testes. They develop gradually as painless testicular enlargements that usually are present several months before being diagnosed. In the single patient with androblastoma and gynecomastia (Teilum), the gynecomastia regressed but did not disappear entirely after removal of the tumor. The other patients showed no recognizable hormonal abnormalities.

Testicular tubular adenomas have been reported in cryptorchids and pseudohermaphrodites. In the army series one tubular adenoma was found in an undescended testis (fig. 84). In addition, there were tubular adenomas associated with four other testicular tumors: a seminoma, an interstitial cell tumor, a choriocarcinoma, and a teratoma. The first two were in undescended testes and the latter two in scrotal testes. The clinical course of these patients is determined by the presence of cryptorchidism or other testicular tumor; the adenomas are usually incidental findings.

GROSS. At the time of diagnosis, mixed and diffuse androblastomas are moderately large tumors, usually over 100 cc., that distend but do not otherwise distort the testicular capsule. On section these tumors appear spherical or ovoid and lobulated in outline with a definite margin and sometimes a definite capsule. They are solid and firm without necrosis or hemorrhage and have a yellow color, which may be diffuse or spotty, with intervening gray-white connective tissue septa.

The testicular abnormalities, i.e., cryptorchidism and/or other testicular tumors with which tubular adenomas are usually associated, dominate the gross appearance of the testis. The adenomas occur as single or multiple, discrete, solid, yellow, round, or oval nodules, 1 to 5 mm. in diameter, that may be located anywhere in the testicular parenchyma.

MICROSCOPIC. Histologic examination reveals that the three types of androblastomas—diffuse stromal, mixed, and tubular—represent three stages of differentiation of the primitive gonadal blastoma. They progress from the undifferentiated stromal type to the differentiated tubular form that closely resembles the structure of the immature testis. Intermediate stages in the differentiation are designated as mixed types.

The undifferentiated stroma is a feltwork of small, closely packed, round, polygonal, or spindle-shaped cells with small, dark nuclei and little cytoplasm, not unlike active adult ovarian stroma (fig. 86). Differentiation of stroma proceeds in two directions: toward formation of tubules and toward formation of Leydig cells. As the tubular orientation of these cell formations increases, the cells lose stromal character and appear more and more epithelial. At first definite solid cords of small, epithelial-like cells lie in the stroma. Later the cords are set off by a basement membrane. Finally, the cords develop a lumen and become tubules and the lining epithelial cells take on more cytoplasm (fig. 87). The tubular epithelial cells are presumed to be

Figure 84.* Tubular adenoma in undescended testis. Circumscribed nodule of small close-packed tubules is characteristic low power appearance. × 48. A. F. I. P. Acc. No. 97674–1.

Figure 85.* High power view of tubular adenoma seen in figure 84. Note uniformity of vacuolated primitive Sertoli cells lining tubules. Resemblance to embryonic testis is apparent. × 400. A. F. I. P. Acc. No. 97674–2.

*From the Armed Forces Institute of Pathology.

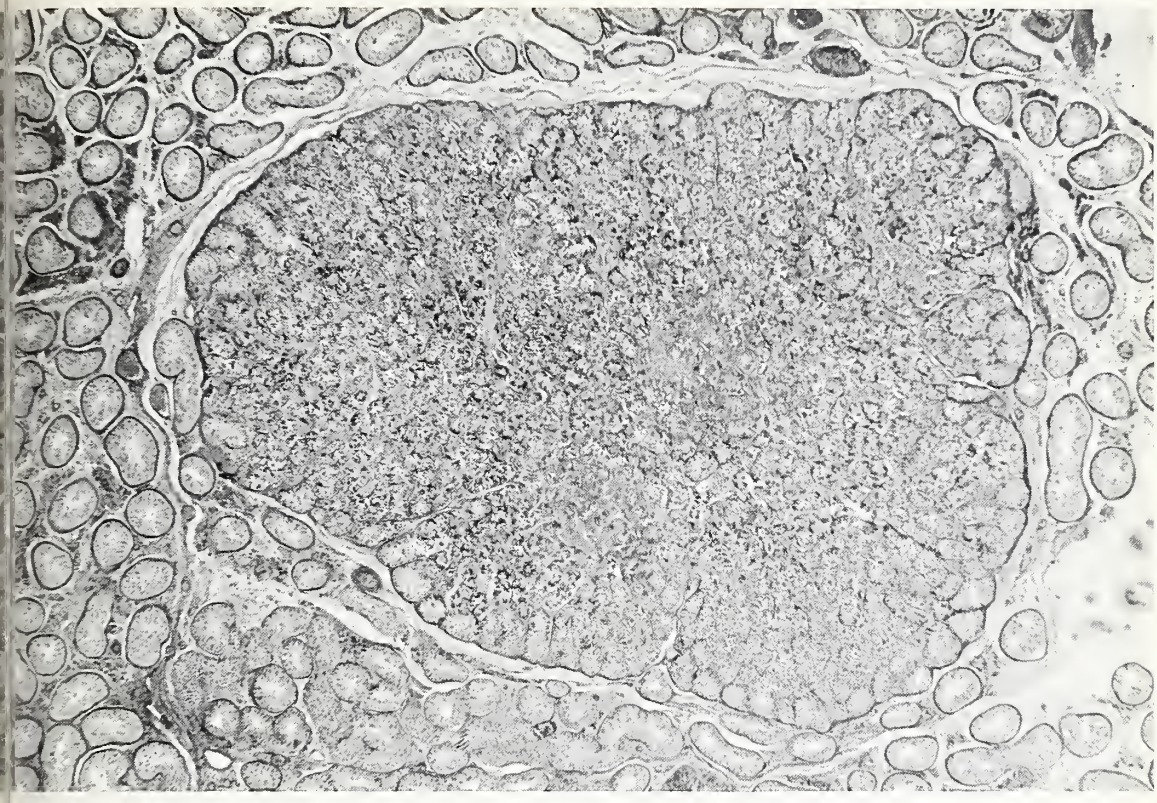

Fig. 84

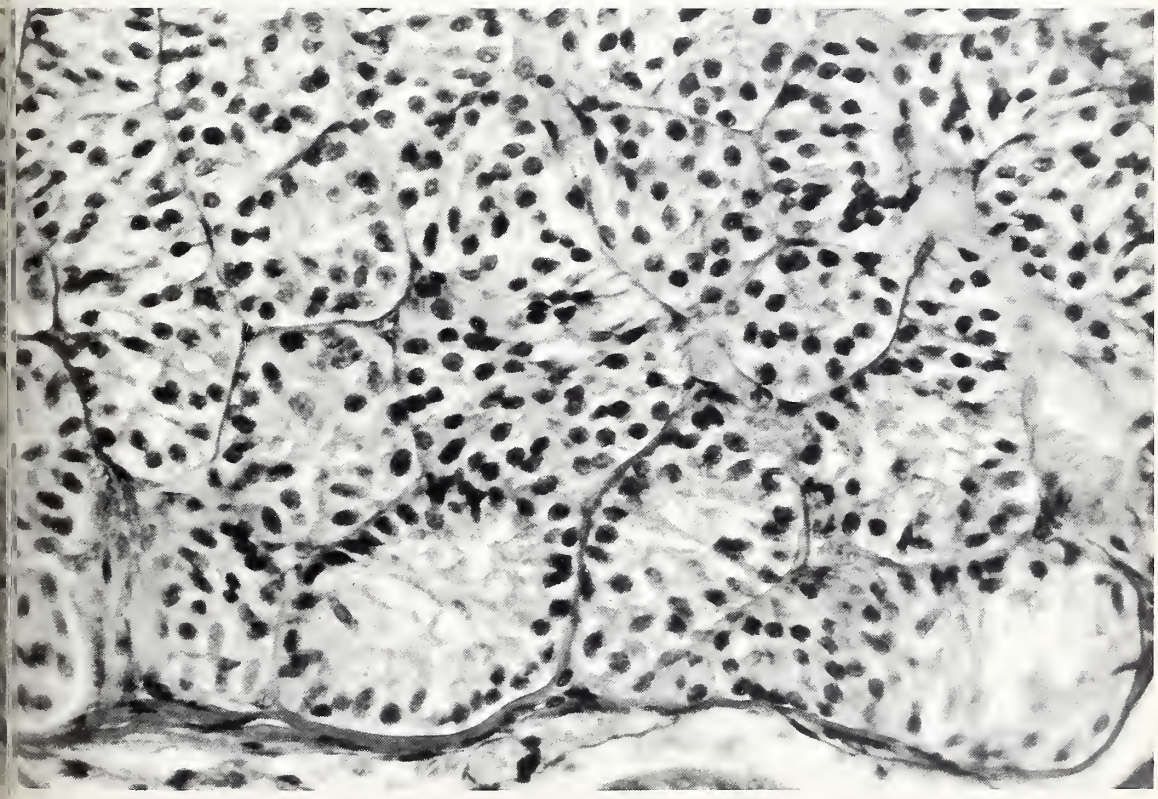

Fig. 85

Figure 86.* Mixed androblastoma. Tubular and stromal components are present. Resemblance to mixed ovarian arrhenoblastoma is striking. × 180. A. F. I. P. Acc. No. 93145.

Figure 87.* Detail of androblastoma. Tumor cells are set off by basement membranes and in some places are oriented about a lumen. There is a definite resemblance to tubular adenoma cells in figure 85. × 400. A. F. I. P. Acc. No. 135763.

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Fig. 86

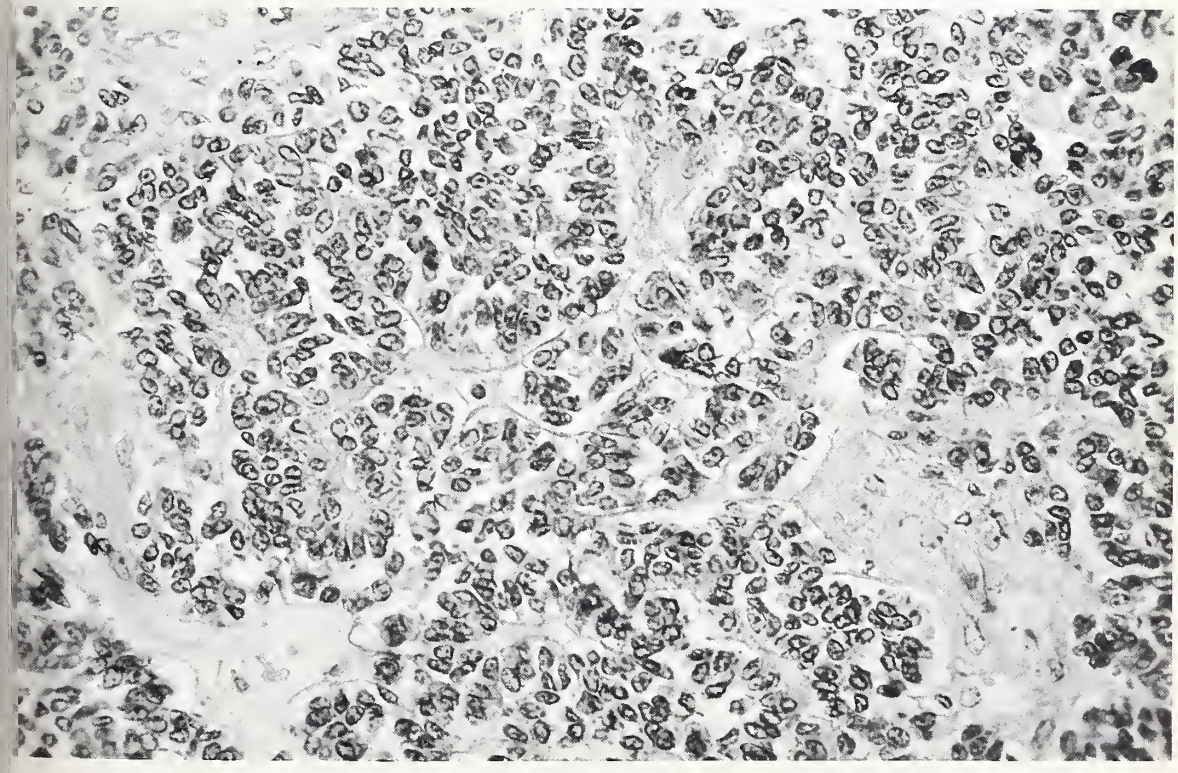

Fig. 87

analogous to Sertoli cells and, therefore, associated with estrogenic activity (Teilum).

Formation of Leydig-like cells, which arise apparently from undifferentiated stromal cells, may be seen in any of the three types of androblastomas but is more frequent in diffuse and mixed types.

Well differentiated tubular adenomas are discrete but unencapsulated nodules of closely packed, uniform, small, intertwining tubules that resemble, strikingly, the structure of the fetal testis (figs. 84, 85). The tubules are outlined by a thin basement membrane, within which are regularly arranged, uniform, small, columnar cells with basal nuclei and light-staining vesicular cytoplasm. The lumina of the tubules vary with different tumors, being most evident in association with most complete differentiation of epithelium and almost nonexistent in less well differentiated tubules. Transitions between adjacent testicular tubules and the tubules of the adenoma have been reported. Few, if any, Leydig cells are found in the scanty stroma.

The tubular epithelium resembles both Sertoli cells and rete epithelium. As Willis points out, there should probably be no sharp separation between Sertoli cells and rete epithelium or between the tumors derived therefrom. In the army series of testicular tumors, there were several instances of encroachment on the rete by tumor, resulting in a hyperplasia of rete epithelium closely resembling the tubules of an adenoma.

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TUMORS OF THE TESTICULAR APPENDAGES — EPIDIDYMIS, SPERMATIC CORD, AND TESTICULAR TUNICS

Introduction

The epididymis is a comma-shaped structure closely attached to the posterior border of the testicle. Near the upper pole of the testicle, 12 to 14 efferent ducts emerge from the rete and form the head of the epididymis. They follow a coiled spiral course and open into the ductus epididymidis, which pursues a tortuous path through the body and tail of the epididymis. At the inferior aspect of the tail of the epididymis, the ductus epididymidis emerges as the ductus deferens which, together with its associated arteries, veins, nerves, and cremaster muscle, forms the spermatic cord. The spermatic cord ascends and passes through the inguinal canal.

The testicular tunics include the tunica albuginea, a dense fibrous membrane immediately surrounding the testis, and the tunica vaginalis propria testis, an extension of the peritoneum, which covers the anterior and lateral surfaces of the testis and is reflected to form a serous cavity surrounding the testis.

With the exception of adenomatoid tumors, which will be considered separately, almost all of the tumors of the appendages are clearly derived from the connective tissues. They will be described under the general categories of benign connective tissue tumors and sarcomas.

The spermatic cord is more frequently involved by tumor than are the other testicular appendages. About 75 percent of extratesticular scrotal tumors are found in the cord. According to the reported cases, about 70 percent of tumors of the appendages are benign and 30 percent malignant. These figures may be somewhat weighted in favor of malignant tumors because some testicular tumors which extensively involved the appendages appear to have been reported as primary in the appendages. The true incidence of malignant tumors is probably closer to 10 to 15 percent of all tumors of the appendages.

Adenomatoid Tumors

SYNONYMS AND RELATED TERMS: "Adenocarcinoma"; adenofibroma; adenofibromyoma; adenoma; adenomyoma; angiomatoid tumor of endothelium; "diffuse lymphangioendothelioma"; fibroma; "lymphadenoma"; "lymphangioma of genital tract"; "lymphangioma simplex"; "lymphatic reticuloendothelioma"; mesothelioma of genital tract (benign); "mixed tumor"; myo-adenofibroma; "myxofibrotic capillary angioma"; nephrogenic adenoma of bladder.

DEFINITION. Adenomatoid tumors are characteristic, small, benign neoplasms peculiar to the genital tracts of both male and female. They are made up of a fibrous stroma in which are found numerous disoriented spaces lined by cells which may resemble endothelium, epithelium, or mesothelium.

Figure 88.* Malignant pleural mesothelioma. While glandlike structures may bear superficial resemblance to those in adenomatoid tumors, the basic differences both cytologically and architecturally are apparent. × 185. A. F. I. P. Acc. No. 218716–18.

Figure 89. High power view of pleural mesothelioma seen in figure 88 to show cells of mesothelial tumor for comparison with adenomatoid tumors in figures 97 and 98. × 520. A. F. I. P. Acc. No. 218716–19.

Figure 90.** Mesothelial papilloma of tunica vaginalis. These mesothelial cells bear little resemblance to cells of adenomatoid tumors. × 395. A. F. I. P. Acc. No. 106180–1.

Figure 91.** Mesothelial downgrowth from tunica vaginalis of testis containing teratoid tumor. Mesothelial cells form glandlike spaces but do not form cords or have intracellular vacuoles, so characteristic of adenomatoid tumors. × 145. A. F. I. P. Acc. No. 176849–2.

*Figure 88 to 91 show undoubted mesothelial proliferations and tumors for comparison with the adenomatoid tumors shown in figure 92 to 98.

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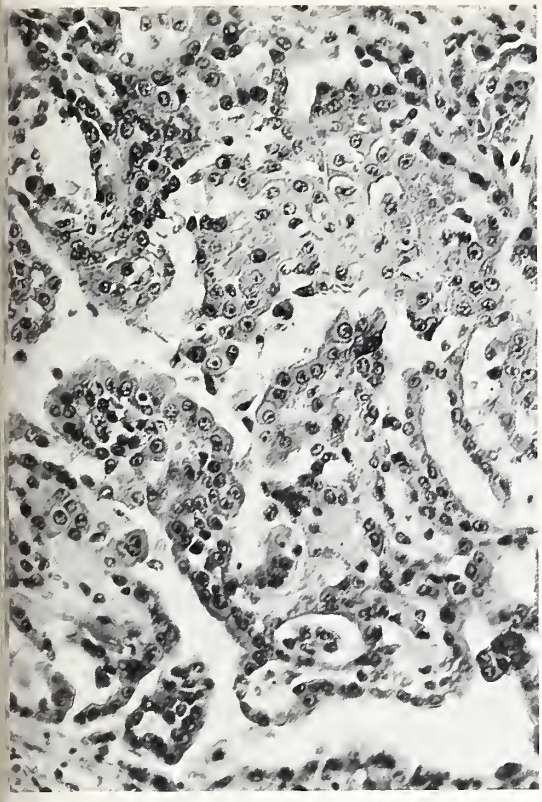

Fig. 88

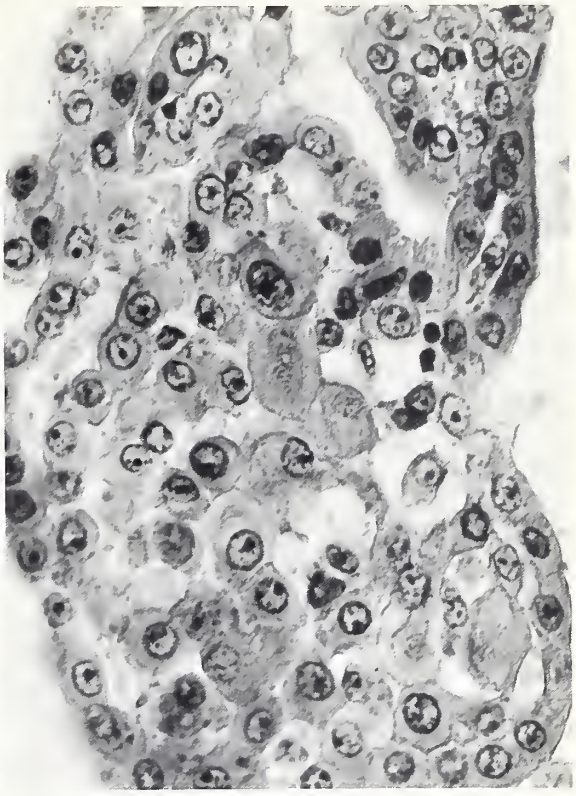

Fig. 89

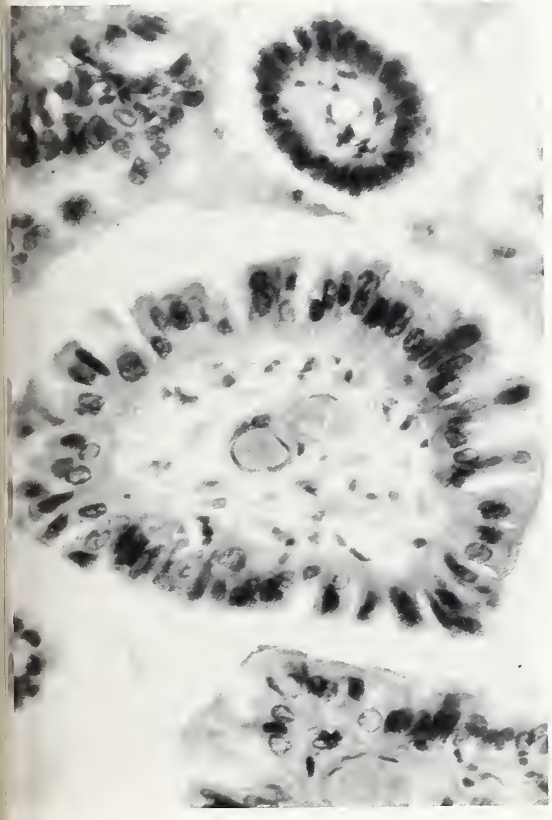

Fig. 90

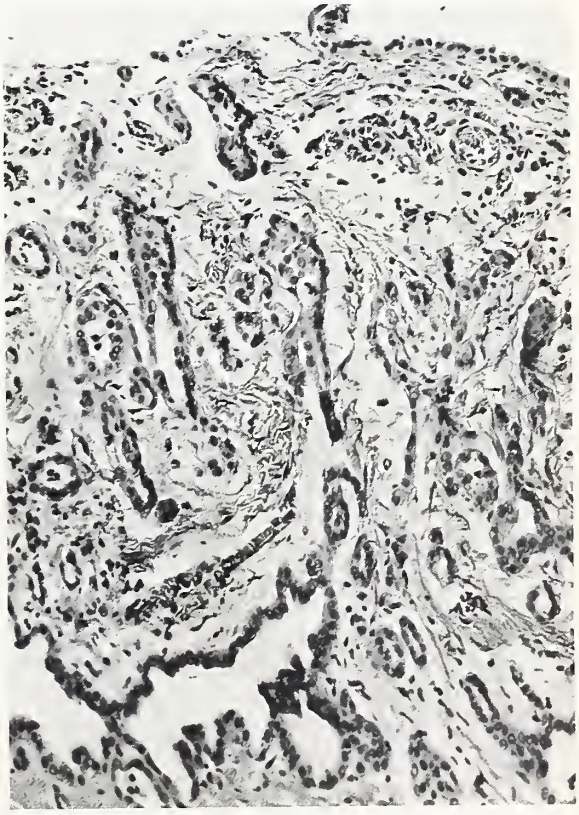

Fig. 91

INCIDENCE. Of the 89 reported instances of adenomatoid tumors, 64 have been in males and 25 in females. These tumors are exceedingly rare before puberty and most frequent between 20 and 40 years of age (Fajers).

There seems to be no relation to trauma, inflammation, or endocrine disturbances.

ORIGIN. Much has been written about the nature and origin of the adenomatoid tumors. As is evident from the list of synonyms, vascular endothelium, mesothelium, wolffian system epithelium, and müllerian duct epithelium have all been considered to be the sources of this tumor. This difference of opinion is, in part at least, because the tumors are relatively rare and vary considerably in histologic appearance. Individual tumors may suggest origin from various of the above sources. However, in our opinion, none of the proposed theories of origin is entirely satisfactory, and we favor the descriptive and noncommittal term **adenomatoid tumor** until more convincing evidence is available.

Adenomatoid tumors in women afford evidence against either müllerian or wolffian origin. Cyclic changes of the genital tract, which would be expected of a müllerian derivative, are lacking. The situation of almost all tumors in women along the fallopian tubes and not in the region of wolffian remnants speaks against the latter origin (Fajers).

Mesothelial origin is perhaps the most acceptable. However, several facts are not in accord with this theory. First, all adenomatoid tumors have been benign and no malignant derivatives have been described, while most tumors arising from pleura and peritoneum are malignant (figs. 88, 89). Second, the characteristic angioadenomatoid pattern of adenomatoid tumors is seldom, if ever, formed in mesotheliomas. Third, no connection between the 40 adenomatoid tumors we have studied and mesothelium have been observed. Fourth, the mesothelial proliferations in the form of papillomatous projections or limited downgrowths of the tunica vaginalis of testes and epididymis, which are seen occasionally in testicular tumors and in inflammations, do not have the histologic appearance of adenomatoid tumors (figs. 90, 91).

COURSE. Only about one quarter of adenomatoid tumors cause pain; the remainder are symptomless. They are solitary, small tumor nodules which show no noticeable growth or only slight enlargement, rarely measuring more than 2 cm. in diameter. Their removal is advisable, if only to rule out the possibility of a malignant tumor. Excision can usually be done without sacrifice of testicle, epididymis, or cord.

GROSS. Eighty percent of adenomatoid tumors are in or immediately adjacent to the epididymis (most often the cauda), while the remainder are in the cord and the testis (fig. 92). Because the cauda of the epididymis, the lower cord, and the lower pole of the testis are the most frequent sites, the

Figure 92. Adenomatoid tumor in typical location. White, homogeneous, ovoid nodule seen at lower left is attached to tail of epididymis. The tumor appears encapsulated and involves adjacent structures only by compression. This was an incidental autopsy finding and had apparently been symptomless. The benign nature of these tumors and absence of testicular involvement certainly make either local removal for histologic diagnosis or biopsy for immediate frozen section diagnosis advisable, because with such tumors the testis can be spared. A. F. I. P. Acc. No. 218716–34.

Figure 93.* Solid cell cord type of adenomatoid tumor. As can be judged from a sizable series of these tumors, this seems to be the earliest histologic type. Solid cell cords with little or no intracellular vacuolization course through a variable amount of fibrous stroma. × 165. A. F. I. P. Acc. No. 283401–1.

Figure 94.* Adenomatoid tumor showing cell cords with slight vacuolization, probably the second stage in the sequence of these versatile tumors. Here a few intracellular vacuoles are present and several cords have been changed to tubules by vacuole coalescence. Tubule lining is cuboidal and easily recognized as derived from the solid cell cords. × 165. A. F. I. P. Acc. No. 84615–3.

Figure 95.* Adenomatoid tumor with marked vacuolation of cell cords. A few cell cords can still be identified, although most of them have been converted into tubules. The tubules are dilated and lined by flattened epithelium. × 165. A. F. I. P. Acc. No. 94094–3.

Figure 96.* Angiomatoid type of adenomatoid tumor, which represents the end result of progressive vacuolation of the solid cell cords. Vacuoles in all cases contain no stainable material with routine, fat, or mucus stains. Further evidence that this type represents the end stage in the above described series is the dense hyalinized connective tissue stroma which suggests an older lesion than those seen above. × 165. A. F. I. P. Acc. No. 154880–5.

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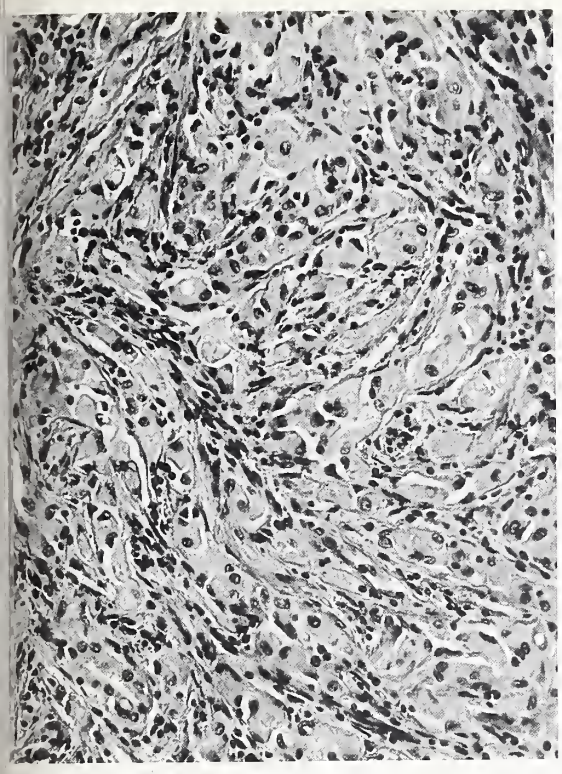

Fig. 93

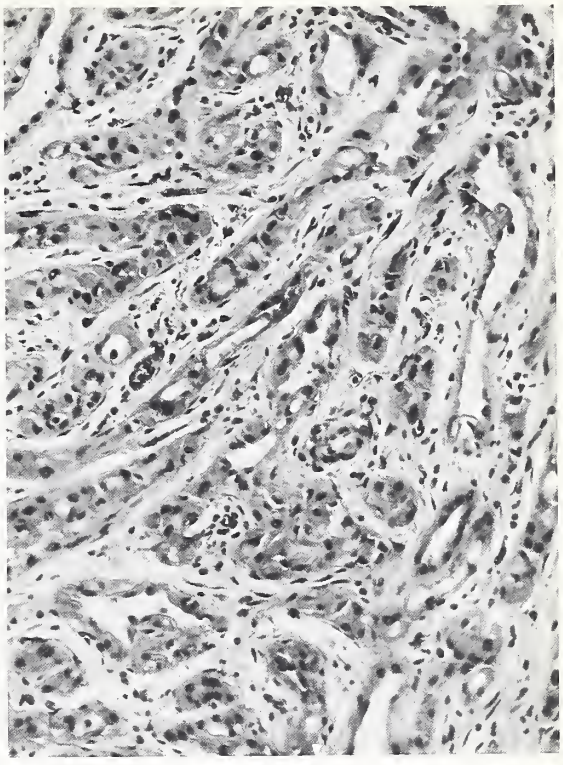

Fig. 94

Fig. 95

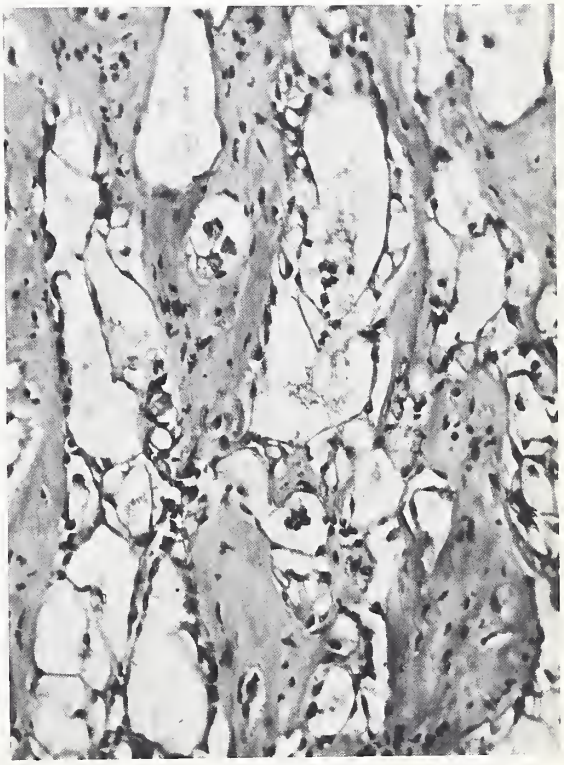

Fig. 96

Figure 97.* High power view of solid cell cord type of adenomatoid tumor showing characteristic cells with acidophilic homogeneous cytoplasm containing rare clear vacuoles and regular round to oval nuclei. × 515. A. F. I. P. Acc. No. 283401–2.

Figure 98.* High power view of well vacuolated adenomatoid tumor showing recognizable remnants of cords now distorted by large intracellular vacuoles. In two cords at the right these vacuoles have coalesced centrally forming a tubular structure with somewhat flattened lining cells. × 515. A. F. I. P. Acc. No. 94094–2.

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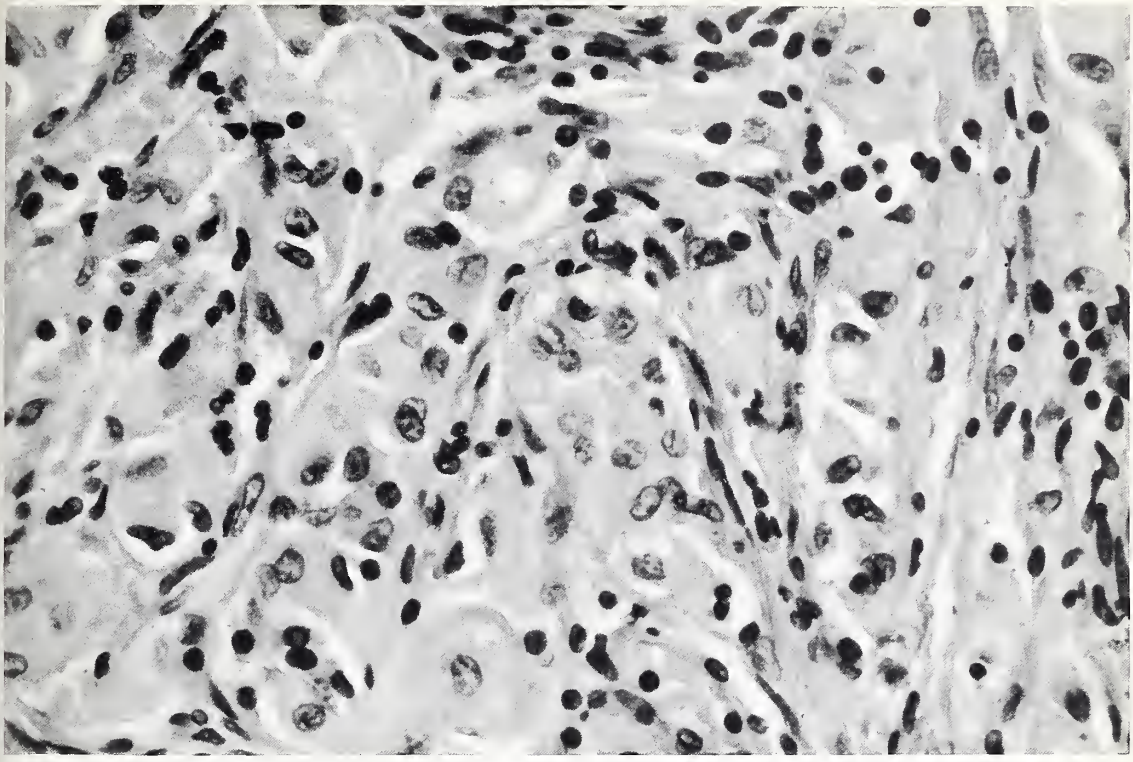

Fig. 97

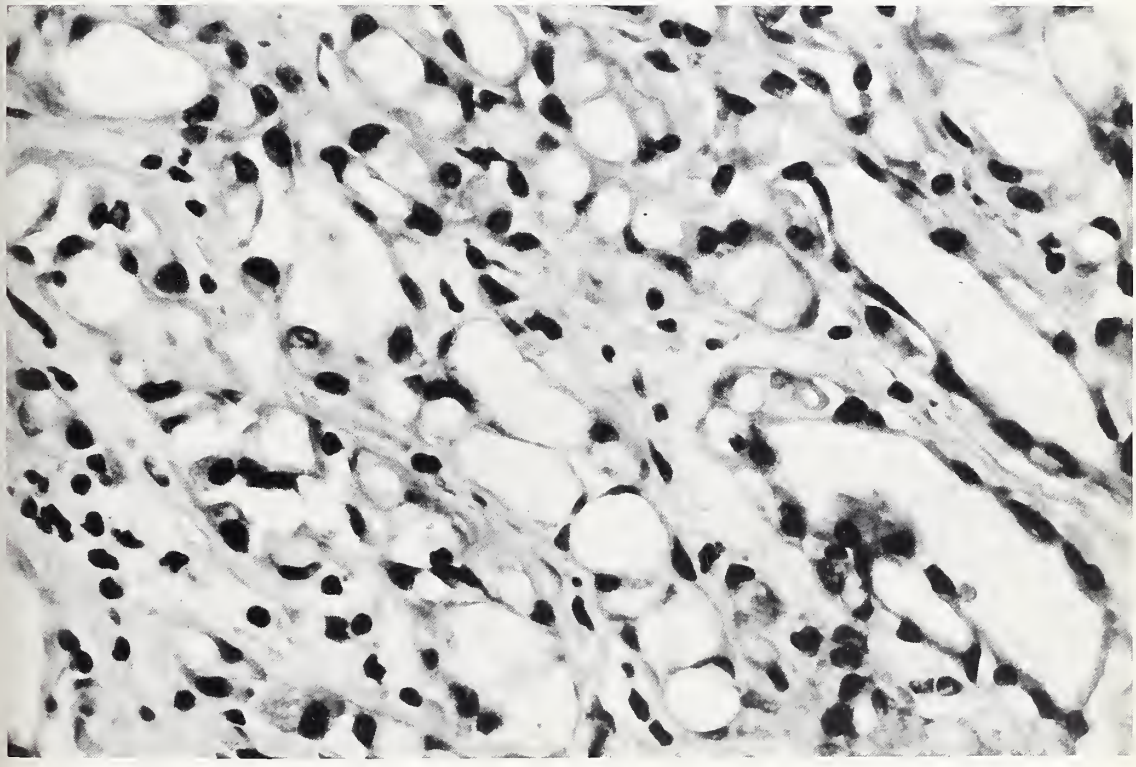

Fig. 98

large majority of these tumors will be found at the posterior inferior aspect of the testis.

They rarely exceed 2 cm. in diameter, are single, ovoid or spherical, smooth, firm, encapsulated, and usually loosely fixed to epididymis, cord, or testis. Cut surface may bulge slightly and has a glistening, gray-white fibrous stroma, in which small yellow foci are occasionally visible.

MICROSCOPIC. The characteristic cell has an acidophilic cytoplasm which is homogeneous except for clear vacuoles of variable size which, in our experience, do not stain for either fat or mucus (see Benign Mesothelioma in Fascicle 5, "Tumors of the Soft Tissues"). The nucleus is medium-sized, round, and uniform, with a definite nuclear membrane, fine homogeneous chromatin, and a central basophilic nucleolus. These cells may be columnar, or cuboidal, forming solid, epithelial-like cords; or they may be flattened and endothelial-like, lining irregular, disoriented spaces. Both cords and spaces are found in most tumors, although a preponderance of one or the other may suggest adenoma or angioma. The cords and spaces are contained in a fibrous stroma.

The development of the angiomatoid spaces from the solid cell cords is easily traced (figs. 93–98). Within the solid cords intracellular vacuoles develop, which enlarge and later coalesce. In the next stage, intermittent large coalescent vacuoles within the once solid cord of cells are surrounded by cuboidal or flattened lining cells, with persistence of segments of the solid cord between them. As the process continues, the vacuoles extend longitudinally along the cord, joining with other small and large vacuoles to form a continuous, somewhat irregular, lumen surrounded by lining cells. At no time is there any stainable material in either intracellular or intercellular vacuoles.

The amount of fibrous stroma varies greatly in different tumors. In some the cords and spaces predominate, separated by thin fibrous septa, while in others fibrous stroma is the predominant element with only occasional small cords or collapsed spaces. Careful search should be made in all so-called fibromas of the testis, epididymis, and cord for inconspicuous adenomatoid elements which will identify these chiefly stromal adenomatoid tumors. The stroma may contain smooth muscle bundles, scattered lymphocytes, plasma cells, mononuclears, and in most tumors lymphoid nodules with secondary germinal centers. The periphery of the tumor is usually composed of compressed collagenous fibers which form a pseudocapsule. The glandlike structures may extend through the capsule or be found between smooth muscle bundles in the periphery of the tumor and give a false impression of invasion.

Benign Connective Tissue Tumors (figs. 99–101)

SYNONYMS AND RELATED TERMS: See Fascicle 5, "Tumors of the Soft Tissues."

The benign tumors are characterized by slow, painless growth with long histories before medical aid is sought.

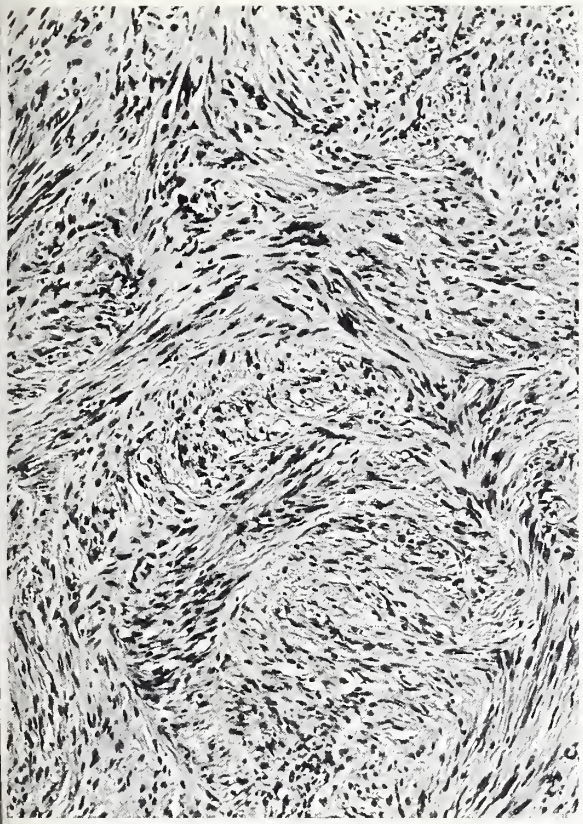

Fig. 99

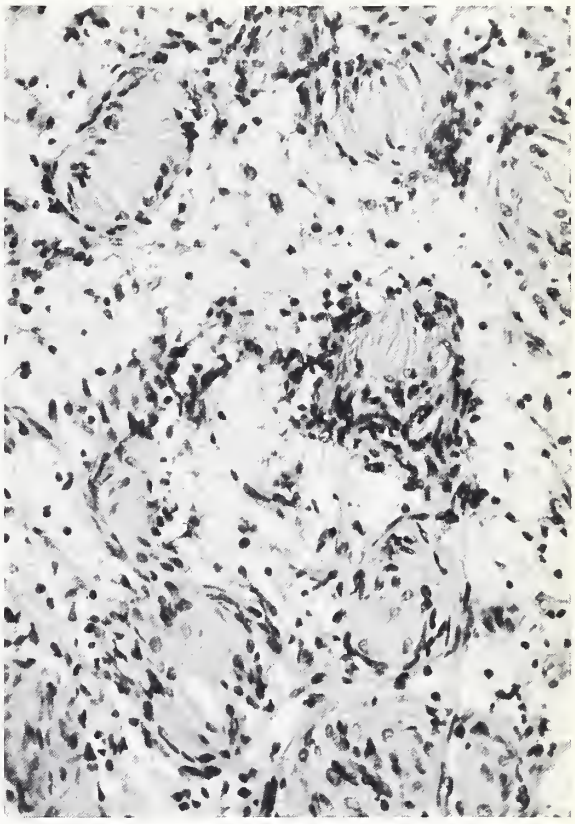

Fig. 100

Figure 99.* Neurilemoma of cord showing characteristic whorled pattern and nuclear palisading. A. F. I. P. Acc. No. 176749–2.

Figure 100.* High power view of area from neurilemoma shown in figure 99. Note formation of structures resembling Meissner's corpuscles. × 220. A. F. I. P. Acc. No. 176749–1.

Figure 101.* Fibroma of tunica. Dense collagenous bands are found with sparse mononuclear infiltration. × 220. A. F. I. P. Acc. No. 104451–2.

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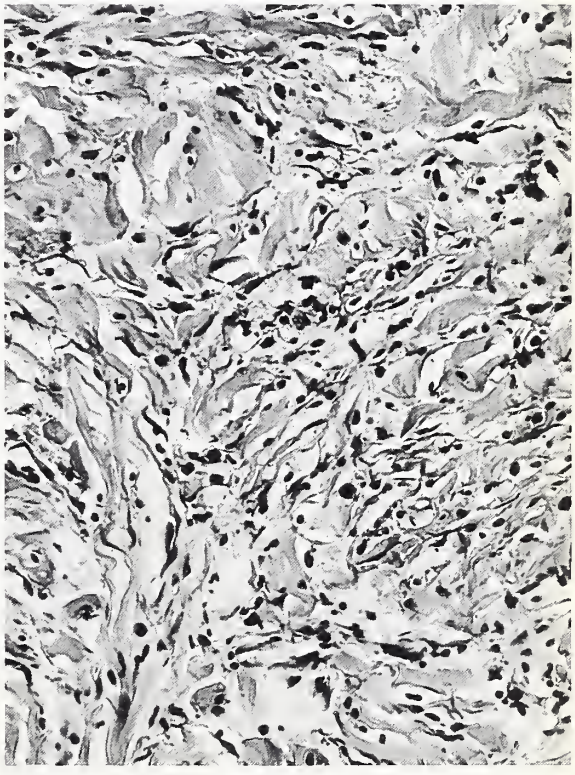

Fig. 101

Lipomas, the most common of these tumors, are found occasionally along the spermatic cord and rarely in the epididymis or testicular tunics. True lipomas of the cord arise from fat within the tunica vaginalis communis. They are usually surrounded by the tunica and derive their blood supply from vessels of the cord. More frequently lipomas of the inguinal canal are encountered. These tumors arise from properitoneal fat in the inguinal canal and may extend along the upper cord into the scrotum. They are connected with and derive their blood supply from the properitoneal fat and lie outside the tunica vaginalis. Grossly, the lipomas may vary considerably in size. They consist of lobulated encapsulated masses of fat which have a characteristic greasy, yellow cut surface. Microscopically, they are seen to consist of normal-appearing fat cells.

Fibromas occur occasionally in the spermatic cord and testicular tunics and rarely in the epididymis (fig. 101). In the cord they are most frequently found near the junction of cord and epididymis. These tumors are usually from 1 to 3 cm. in diameter, ovoid or spherical, firm, discrete, and apparently encapsulated. On section they have a gray fibrillar surface which may bulge slightly. Microscopically, they show variable amounts of dense collagen between the fibroblasts. The blood vessels are thick-walled and at times appear to be undergoing obliteration. Occasional small clumps of mononuclear cells and irregular foci of calcification are seen.

Leiomyomas are extremely rare, being found only in cord and epididymis. These tumors are firm, discrete nodules which grossly resemble closely the fibromas. Microscopically, they can usually be recognized by the characteristic spindle-shaped cells. If, however, a fair amount of collagen has been deposited in the tumors, its differentiation from a fibroma may be very difficult and necessitate differential staining.

Sarcomas (figs. 102–104)

SYNONYMS AND RELATED TERMS: See Fascicle 5, "Tumors of the Soft Tissues."

Sarcomas of the testicular appendages occur relatively frequently in children and young adults. They are usually found low in the cord well within the scrotum instead of in the upper cord and inguinal canal, as in the case of lipomas. The sarcomas grow rapidly and often attain a large size (10 to 15 cm. in diameter). They are usually intimately attached to the structures from which they arise and may invade adjacent tissues so extensively that the exact site or origin is impossible to determine. Recurrences after removal are common, and metastases by blood stream are not unusual.

Almost all varieties of sarcoma have been described in the testicular appendages. The more common types have been rhabdomyosarcoma, leiomyosarcoma, and fibrosarcoma.

Rhabdomyosarcomas arise from the cord. They are usually large and

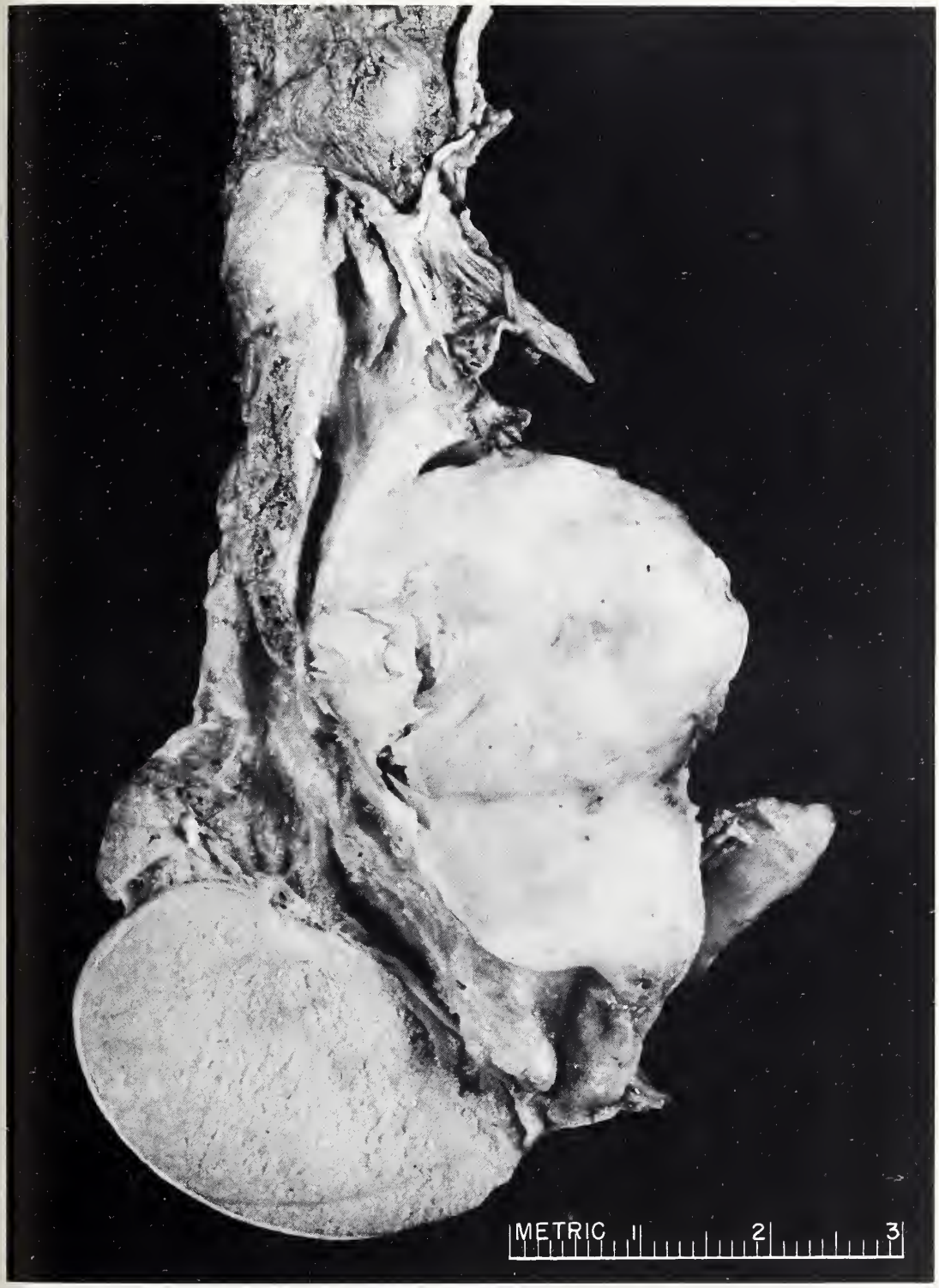

Figure 102. Myosarcoma of the lower end of the spermatic cord. Tumor has been sectioned and appears as a white ovoid mass, slightly larger than, and immediately above, the testis. Fixation of tumor to testis without actual infiltration of testis is common. (From Friedman, N. B., and Ash, J. E. Atlas of Genitourinary Pathology. Washington, D.C.: American Registry of Pathology, 1946.) A. F. I. P. Acc. No. 149068–1.

Figure 103.* Leiomyosarcoma of cord. Characteristic large plump spindle cells are close-packed and have little connective tissue stroma. Mitotic figures and tumor giant cells are not infrequent. × 475. A. F. I. P. Acc. No. 199636–2.

Figure 104.* Rhabdomyosarcoma of cord. Tumor giant cells with abundant eosinophilic cytoplasm are conspicuous. Some of these giant cells form elongated fibers which occasionally have cross striations. × 475. A. F. I. P. Acc. No. 149068–2.

*From the Armed Forces Institute of Pathology.

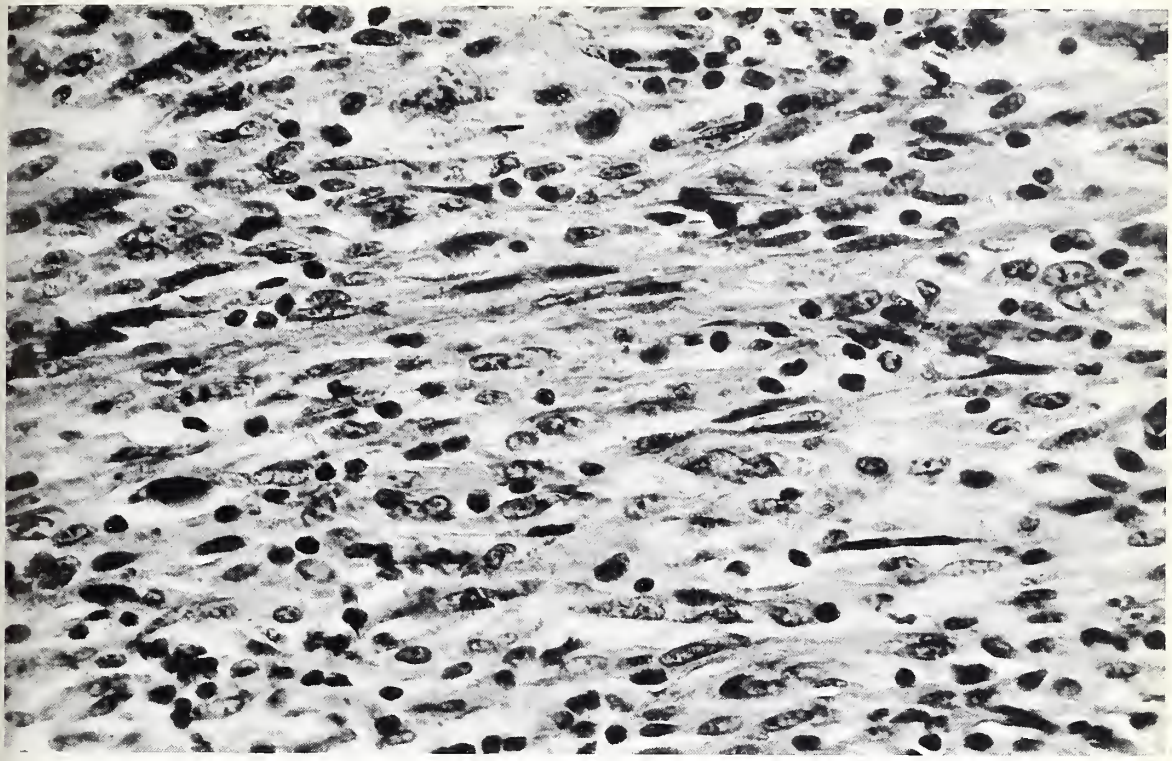

Fig. 103

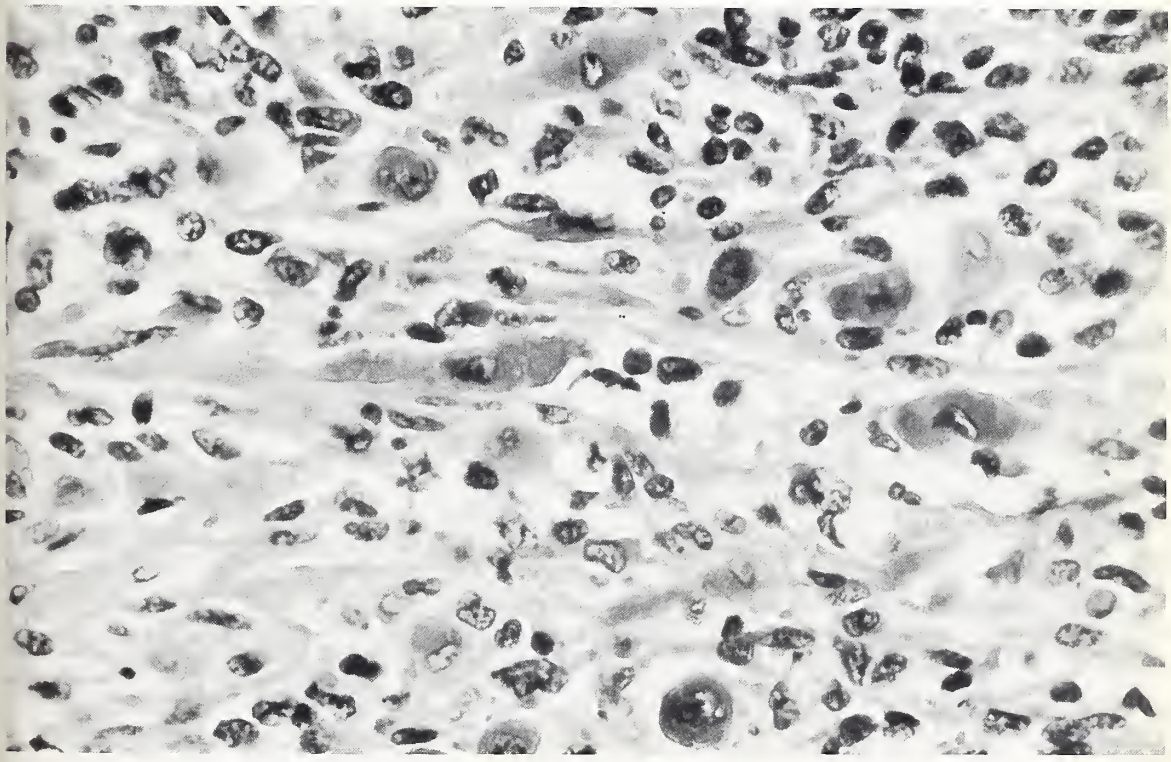

Fig. 104

frequently invade or compress the testis (fig. 102). They are nonencapsulated, soft to rubbery tumors, which on section bulge slightly and have a tan to red-brown color. Foci of degeneration and hemorrhage are occasionally seen. Microscopically, the characteristic features are large, irregular, multinucleate giant cells, some of which may be ribbon or banjo shaped and may have cross striations similar to those seen in normal striated muscle (fig. 104). These striations are often inconspicuous in sections stained with hematoxylin and eosin, but may be brought out in phosphotungstic acid-hematoxylin preparations. The remaining tumor cells are markedly pleomorphic and anaplastic and have numerous mitoses.

Leiomyosarcomas are similar to the rhabdomyosarcomas grossly, except that the cut surface of the former is usually white to gray and slightly firmer. The characteristic cell is a spindle-shaped smooth muscle cell. Bizarre giant cells are not uncommon, and numerous mitoses are usually evident (fig. 103). The cells may at times palisade and at other times form a herringbone pattern.

Fibrosarcomas resemble the leiomyosarcomas grossly. Microscopically, these tumors show great variation, from a low-grade picture of malignancy with little anaplasia, few mitoses, and moderate collagen formation to a high grade of malignancy with much mitotic activity, extreme anaplasia with giant cells and little evidence of collagen formation. Some evidence of collagen formation by tumor cells is a prerequisite for this diagnosis (see Fascicle 5, "Tumors of the Soft Tissues").

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TUMORS OF THE URETHRA (Originally planned as Fascicle 31b)

Introduction

The urethra has prostatic, membranous, and cavernous portions. The membranous portion is contained largely within the urogenital diaphragm and the cavernous within the corpus cavernosum urethrae. In cross section the prostatic portion is U-shaped, accommodating the colliculus seminalis, onto which open the ejaculatory ducts and prostatic utricle (homologue of the lower vagina in the female). Transitional epithelium forms the lining of the prostatic portion, while the membranous and cavernous portions are lined mainly with pseudostratified or stratified columnar epithelium. Stratified squamous epithelium, however, lines the fossa navicularis and appears in scattered patches in the cavernous portion. The urethral mucous membrane has many outpocketings which continue into branching tubular glands of Littré.

Papilloma

SYNONYMS AND RELATED TERMS: Papillary adenoma; papillary polyp; polyp; simple polyp; glandular polyp; adenomatous polyp; benign polyp.

Papillomas occur anywhere along the urethra but most frequently in the posterior urethra near the neck of the vesicle. Solitary papillomas occur most frequently in the bulbar portion of the cavernous urethra, while multiple papillomas are most common near the vesical orifice and external meatus. Early in their course they cause urinary obstruction and hematuria. Papillomas vary from flat, sessile warts to bulky, exuberant growths or long, frondlike strands (fig. 105). They are soft and friable and usually red (Lowsley and Kirwin). Transitional epithelium usually covers the connective tissue cores of the papillomas (figs. 106, 107). Less frequently, usually in papillomas of the fossa navicularis or in the presence of infection, the epithelium will be stratified squamous.

Carcinoma

SYNONYMS AND RELATED TERMS: Epidermoid carcinoma; transitional (cell) carcinoma.

INCIDENCE. Carcinoma of the urethra is rare. Only 216 cases have been reported in the literature. About 85 percent of these tumors occurred in the fifth, sixth, and seventh decades, with a peak incidence of 40 percent in the sixth decade.

ETIOLOGY. The frequency with which urethral strictures precede carcinoma of the urethra (76 percent of patients with adequate history) suggests that they may play an etiologic role in development of carcinoma (Kreutzmann and Colloff). The most frequent sites of strictures—the cavernous and membranous portions of the urethra—are also the most frequent sites of carcinoma. It is well known that strictures with their associated infection and ir-

Figure 105. Sagittal section of penis and penile urethra showing multiple papillomas. There is no gross focus of infiltrative growth. (From Friedman, N. B., and Ash, J. E. Atlas of Genitourinary Pathology. Washington, D.C.: American Registry of Pathology, 1946.) A. F. I. P. Acc. No. 95801.

Figure 106.* Transitional cell papilloma of urethra. Note fine frondlike projections and uniform nature of epithelial covering. × 62. A. F. I. P. Acc. No. 262561–2.

Figure 107.* Higher power view of papilloma seen in figure 106 to show the regular uniform type of epithelial cell which makes up this tumor. Resemblance to bladder papillomas is obvious. × 205. A. F. I. P. Acc. No. 262561–1.

*From the Armed Forces Institute of Pathology.

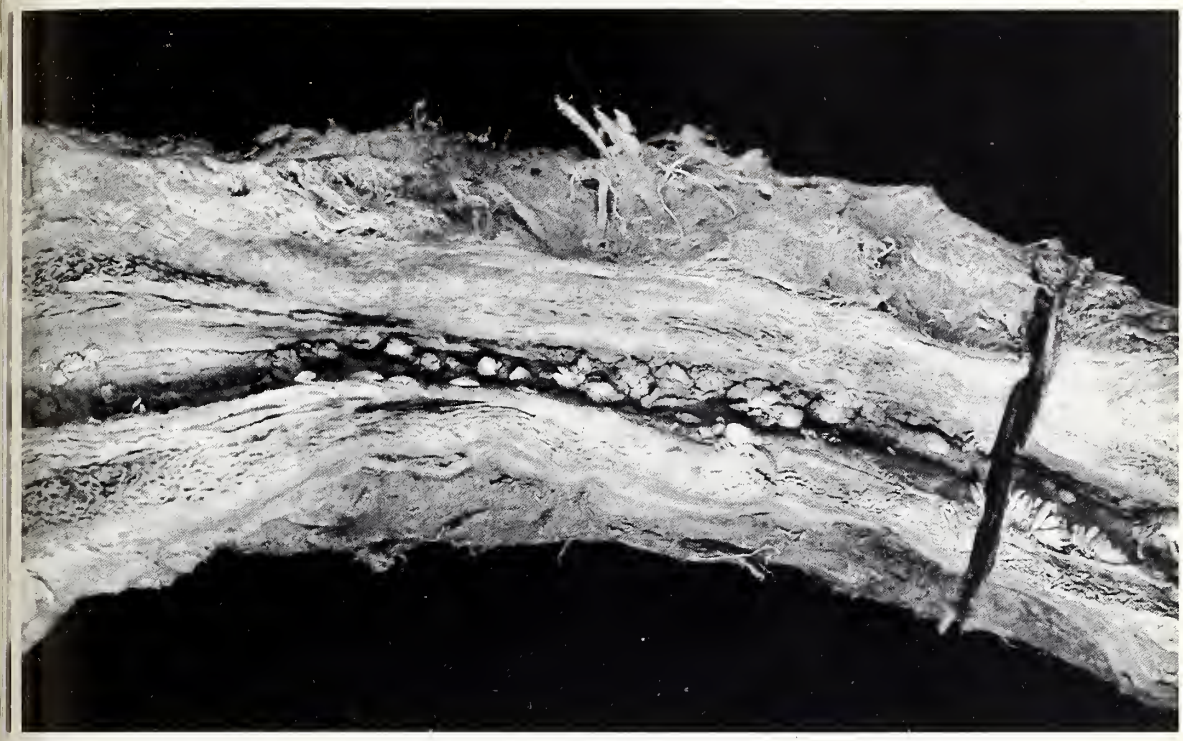

Fig. 105

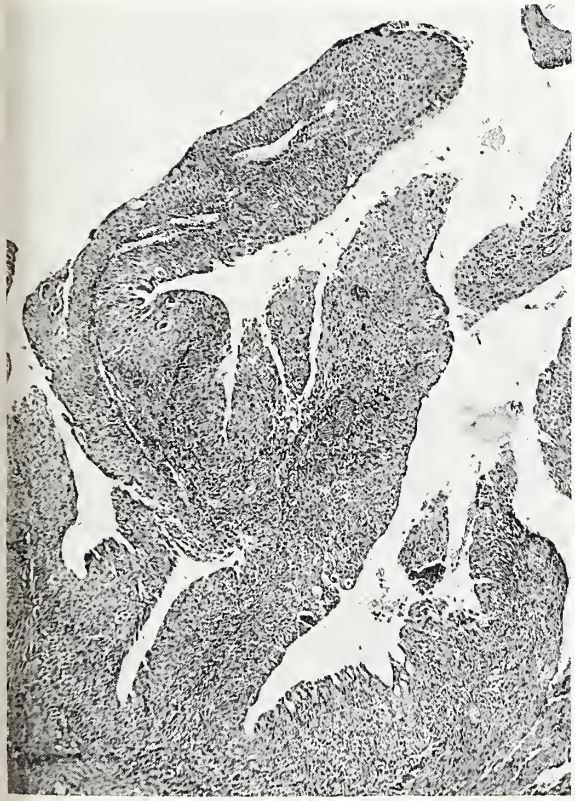

Fig. 106

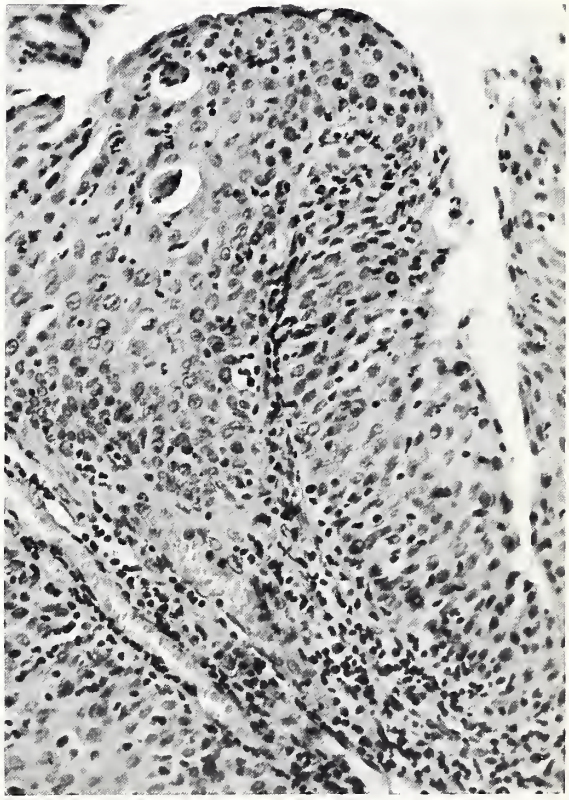

Fig. 107

ritation cause squamous metaplasia of the columnar epithelium of the urethra. Because the normal epithelium is chiefly columnar, foci of squamous metaplasia would seem a likely point of origin for the predominantly epidermoid carcinomas of the urethra.

COURSE. The first indication of carcinoma of the urethra is urinary obstruction, often with hematuria and a purulent discharge. Posterior urethral tumors may later form a fluctuant mass, frequently associated with fistulas, in the perineal midline posterior to the penoscrotal angle. Carcinomas of the anterior urethra usually become palpable on the ventral surface of the penis early in their course. Both lymph-borne and blood-borne metastases may occur relatively early.

Prognosis for urethral carcinoma varies with location of the tumor and presence or absence of metastases at time of treatment. Anterior urethral tumors have a definitely better prognosis than posterior urethral tumors, no doubt partly because of earlier detection and a better chance of complete excision. No survival or cure rates are available.

GROSS. Carcinoma may occur anywhere in the urethra. The distribution of lesions in the various parts of the urethra is as follows: fossa navicularis, 19 percent; anterior or penile urethra (except fossa navicularis), 26 percent; posterior or bulbomembranous urethra, 55 percent.

Carcinomas of the bulbomembranous portion of the urethra infiltrate the corpora cavernosa extensively, and when diagnosed are frequently from 2 to 3 cm. in diameter. The mucosal surface in the region of the tumor usually ulcerates so that the structure of the urethra can no longer be identified. Later, infection and necrosis of the tumor result in a semifluctuant mass in the perineal midline. The cut surface of the tumor commonly has the white granular appearance characteristic of epidermoid carcinoma.

Anterior urethral carcinomas commonly form a palpable nodular or indurated mass with cutaneous urethral fistulas on the ventral surface of the penis. These tumors cause destruction of urethral mucosa and infiltrate the corpora spongiosa. They are contained for a time by the tunica albuginea, but finally invade the corpora cavernosa and skin. If the growth involves the fossa navicularis, there may be ulceration of the glans or a tumorous protrusion from the meatus (Kreutzmann and Colloff).

MICROSCOPIC. Urethral carcinomas are epidermoid in 88 percent of cases and papillary, glandular, transitional, or columnar cell in 12 percent. Histologically, the epidermoid carcinomas are almost all of moderate malignancy (Zaslow and Priestley). Finger-like projections of tumor invade adjacent tissues widely and may extend into some of the numerous cavernous blood spaces of the penis. The tumor cells show little keratinization, definite anaplasia, and moderate mitotic activity with atypical mitoses. There is al-

most always a marked chronic inflammatory process associated with the tumor (figs. 108–111).

METASTASES. Lymphatic spread of urethral carcinoma is a frequent, early occurrence. Tumors of the anterior urethra characteristically metastasize to the inguinal nodes, while tumors of the posterior urethra metastasize to the external iliac, hypogastric, and common iliac nodes.

In spite of the frequent invasion of the cavernous blood spaces in the periurethral tissues by carcinoma, tumor spread via the blood stream is not common. A few cases of metastases to the lungs and liver have been reported.

Sarcoma

SYNONYMS AND RELATED TERMS: See Fascicle 5, "Tumors of the Soft Tissues."

Sarcoma of the male urethra is exceedingly rare: only nine cases have been reported. In these there was no site of predilection. The tumors were classed as: fibrosarcoma (2), lymphosarcoma (2), myxosarcoma (2), round cell sarcoma (2), and carcinosarcoma (1). The age distribution was of interest: seven of the nine cases occurred before the age of 25 and the remaining two cases after 65 (Bailey).

These sarcomas involved the corpora cavernosa extensively and produced urethral obstruction. Metastases first occurred in the inguinal region and then spread widely. One recovery and five deaths from sarcoma are recorded.

Tumor-like Lesions

Periurethral glandular nodules of hyperplastic prostates may occasionally protrude into the urethra. These nodules may be either sessile or pedunculated and have been mistaken for adenomas of the urethra. Microscopic examination reveals their structure to be typical of nodular hyperplasia of the prostate. The hyperplastic rather than neoplastic nature of this lesion is discussed in the section on prostate.

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Figure 108.* Epidermoid carcinoma of urethra. Note sheetlike growth of tumor, large keratinized cells, numerous mitoses, anaplasia, and inflammatory infiltrate. The latter frequently follows surface ulceration of tumor. × 185. A. F. I. P. Acc. No. 264672–1.

Figure 109.* High power view of epidermoid carcinoma seen in figure 108. Note variation in cell size, giant cells, cells with clear cytoplasm, absence of frank pearl formation, and infrequent intercellular bridges. These features, together with the single scattered large keratinized cells seen in figure 108, are more common in epidermoid carcinomas originating from mucous membranes than in those which arise from keratinized epithelium. × 395. A. F. I. P. Acc. No. 264672–2.

Figure 110.* Transitional cell carcinoma of the urethra. Characterized at this power by regular oval cells, which tend to palisade along connective tissue septa, and by complete absence of keratinization. × 165. A. F. I. P. Acc. No. 218969–1.

Figure 111.* High power view of transition cell carcinoma seen in figure 110. Note regular, rather uniform-staining, oval, closely packed nuclei and peripheral palisading. × 395. A. F. I. P. Acc. No. 218969–2.

*From the Armed Forces Institute of Pathology.

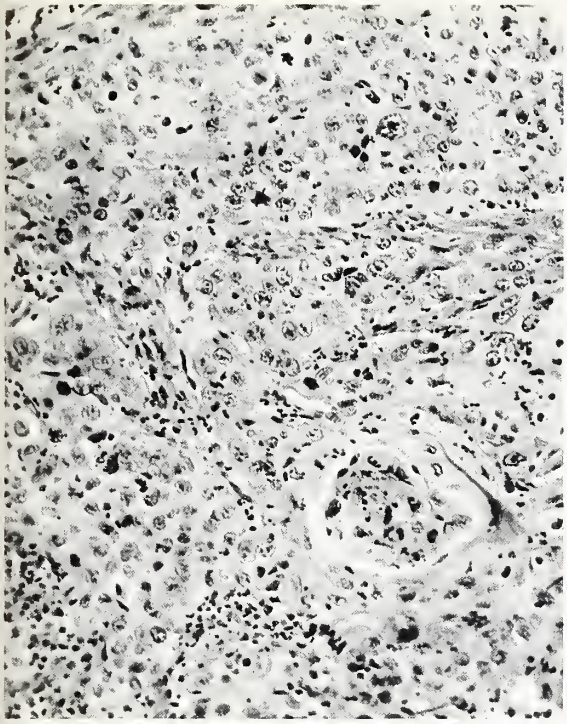

Fig. 108

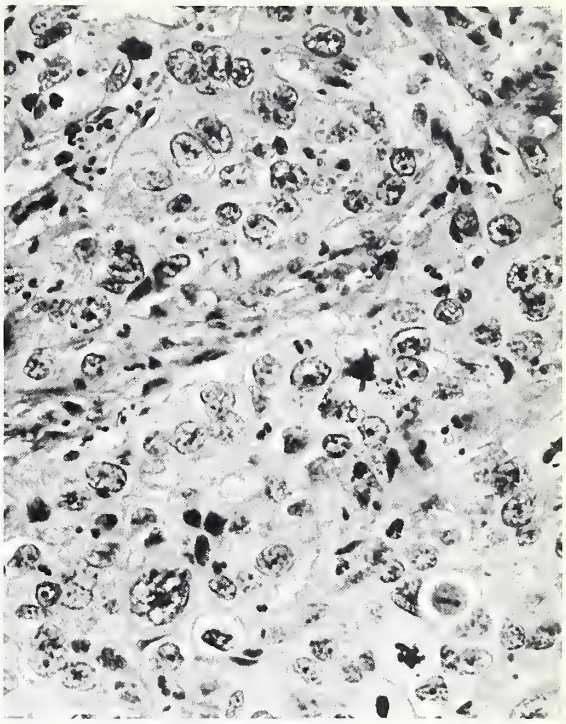

Fig. 109

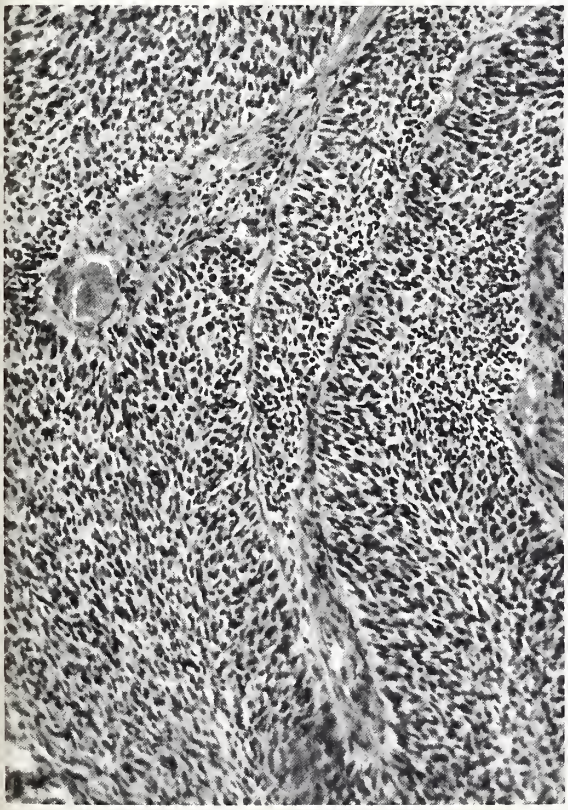

Fig. 110

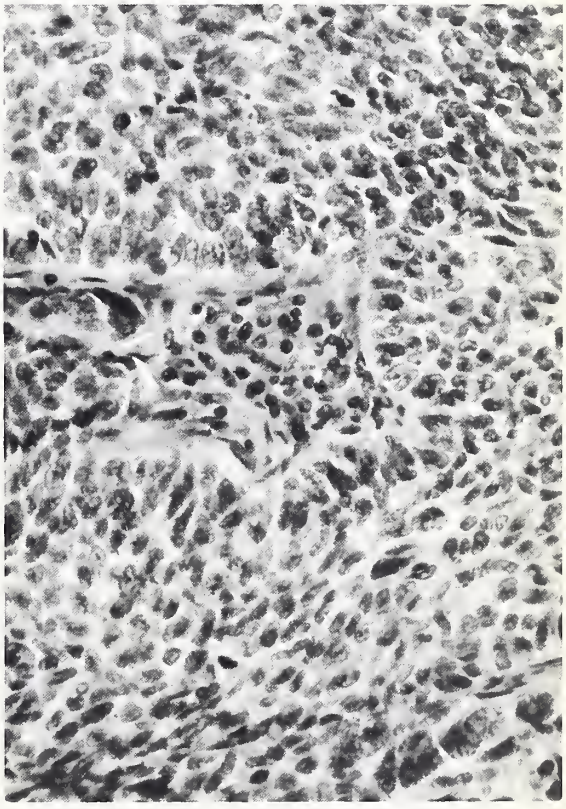

Fig. 111

TUMORS OF COWPER'S GLANDS

Cowper's glands, or the bulbo-urethral glands, are paired, pea-sized structures located within the urogenital diaphragm, which drain by ducts into the floor of the bulbar urethra. They are compound tubulo-alveolar glands with cuboido-columnar alveolar epithelium, which secretes a mucinous material.

Primary tumors of Cowper's glands are extremely rare. Only six cases are reported in the literature. These cases had no characteristic age distribution or clinical behavior. Grossly, they were locally invasive and tended to recur after resection. Microscopically, they were adenocarcinomas with low columnar mucus-secreting cells lining alveoli and tubules and forming a racemose pattern (figs. 113,114).

Gross differentiation of Cowper's gland carcinomas from carcinomas of the posterior urethra is difficult since these tumors may envelop the urethra and invade it. It is possible that some of the adenocarcinomas of the posterior urethra may arise in Cowper's glands.

Reference

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Figure 112. Perineal view of carcinoma of Cowper's gland with extension and involvement of perineal skin causing ulceration. (Courtesy of Dr. L. V. Ackerman, Washington University School of Medicine.) A. F. I. P. Acc. No. 218705.

Figure 113.* Adenocarcinoma of Cowper's gland showing involvement of skin. × 75. A. F. I. P. Acc. No. 218716–14.

Figure 114.* Higher power view of adenocarcinoma of Cowper's gland seen in figure 112 to show nature of acinar structure. × 165. A. F. I. P. Acc. No. 218721–1.

*Courtesy of Dr. L. V. Ackerman, Washington University School of Medicine.

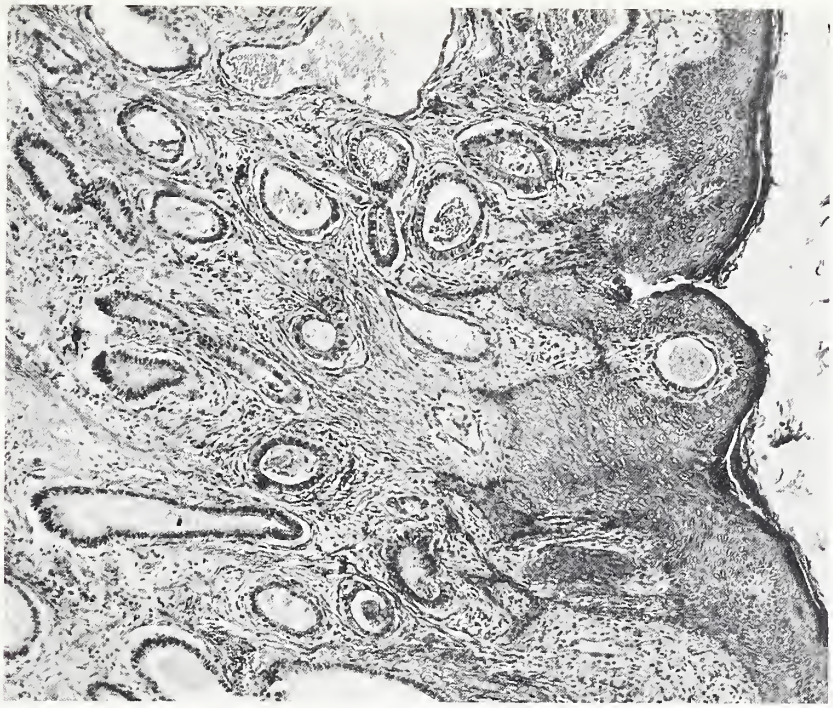

Fig. 113

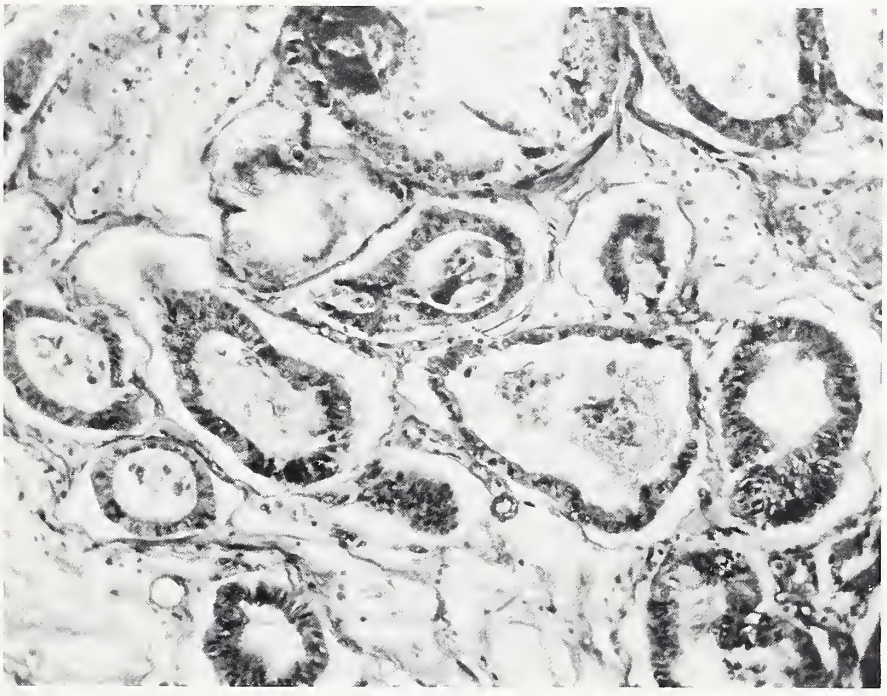

Fig. 114

TUMORS OF THE SEMINAL VESICLES

Introduction

The seminal vesicles are saclike outpouchings from the vasa deferentia at the termination of the latter in the ejaculatory ducts. They have irregular, branching lumens with numerous outpocketings lined by a pseudostratified epithelium, which often contains yellow pigment and secretory granules. The vesicular wall is composed of smooth muscle similar to, but thinner than, that forming the wall of the vas. The vesicles are dependent upon testicular hormone for full development and after castration they atrophy markedly, a phenomenon reversible by injection of androgens.

Tumors of the seminal vesicles are rare. Only 26 cases of carcinoma, two cases of sarcoma, and three benign myomas have been reported. Of the reported carcinomas, slightly less than one half did not involve the prostate, and in these tumors origin in the vesicles was clear. In the remainder there was prostatic invasion, making differentiation from prostatic tumors difficult and rarely without question.

It is curious that two structures such as the seminal vesicles and prostate, arising from the same embryonic anlage and responding to the same hormonal stimuli, should differ so much in the frequency with which they give rise to tumors.

Carcinoma of the Seminal Vesicles

SYNONYMS AND RELATED TERMS: Adenocarcinoma; papillary adenocarcinoma; undifferentiated carcinoma.

DEFINITION. A malignant tumor arising from the epithelial lining of the seminal vesicles.

INCIDENCE. Of 20 reported cases with ages stated, 6 have occurred in the fourth decade, while the remaining 14 were scattered rather uniformly in the sixth through ninth decades.

COURSE. Late in their course these tumors usually cause urinary retention, dysuria, or hematuria. Only one case has shown early symptoms and has been diagnosed soon enough to allow complete resection. In the remaining cases the prognosis has been poor, with local invasion or metastases frequently present at time of diagnosis and death resulting within a year of onset of symptoms.

GROSS. The tumor completely replaces the vesicle and invades locally in over half the cases, involving the opposite vesicle, the prostate, and the floor of the bladder with about equal frequency. Obstruction of the prostatic urethra, internal urethral meatus, or lower portions of one or both ureters is

common. Extension to the rectum is a rare occurrence. The tumors attain a large size, frequently forming a mass from 10 to 15 cm. in diameter.

MICROSCOPIC. These tumors apparently arise from the lining epithelium of the vesicles and are for the most part adenocarcinomas. Thirteen cases have been reported as adenocarcinoma, some with papillary tendencies, and four as undifferentiated carcinomas. The adenocarcinomas are relatively well differentiated, composed of rather clear columnar cells forming acini and in some instances papillary projections.

METASTASES. Metastases are present in about two thirds of the cases. Regional lymph nodes, bones, and lungs are the most frequent sites.

DIFFERENTIAL DIAGNOSIS. Tumors of the seminal vesicles may be misdiagnosed because of their rarity. They must be differentiated from prostatic carcinoma, rectal carcinoma, and metastatic rectal shelf tumors. The microscopic picture is suggestive because of its frequent adenopapillary structure but not distinctive enough to allow positive histologic diagnosis and absolute differentiation from the far more frequent prostatic carcinoma. As a result, history as well as clinical and gross findings must be used in establishing the diagnosis. The absence of invasion of the rectal mucosa by seminal vesicle carcinoma will differentiate it from primary rectal carcinoma. Frequent invasion of structures of the urinary tract by seminal vesicle carcinoma aids in differentiation from metastatic rectal shelf tumors, which rarely involve the urinary tract (McCrea).

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TUMORS OF THE PENIS

Introduction

The penis is made up of three cylindrical bodies of cavernous erectile tissue: two corpora cavernosa penis and a corpus cavernosum urethrae. The latter is coursed throughout by the urethra and terminates in a caplike enlargement, the glans, which covers the distal ends of the corpora cavernosa penis. The specialized skin of the penis is thin, free of fat, and contains much smooth muscle. The skin of the shaft is projected into a tubular fold, the prepuce, which covers the glans.

Neoplasms of the penis arise almost entirely from the epithelium and in general are similar to tumors arising elsewhere in skin and mucous membranes.

Premalignant Lesions and Preinvasive Carcinoma

SYNONYMS AND RELATED TERMS: Carcinoma in situ; erythroplasia of Quèyrat; leukoplakia.

Leukoplakia, erythroplasia of Queyrat, and carcinoma in situ are all associated with the genesis of carcinoma. They occur in many sites, and only erythroplasia is primarily a disease of the penis. The exact incidence of these lesions and the frequency with which they precede invasive carcinoma are unknown, although clinical observations attest to the frequent relation of the two.

Leukoplakia is a chronic inflammatory, premalignant lesion which occurs most frequently in the oral mucous membranes and rarely in the penis. In the latter site it usually appears as a white, rough or pearly, superficial patch of thickened epithelium on the glans or prepuce. Microscopically the epithelium shows hyperkeratosis, marked acanthosis, and chronic inflammation (fig. 115). The vessels of the dermis are enlarged, the papillae are edematous, and there is an infiltration of lymphocytes and plasma cells.

Erythroplasia of Queyrat is usually considered to be a premalignant lesion, although the frequency with which it precedes or is associated with carcinoma has induced some observers to consider it a variety of carcinoma in situ. Extremely rarely it may develop on the vulva or lip, but usually it appears on the glans penis as single or multiple, well defined, velvety red plaques of epithelial induration with smooth surfaces and slightly raised rolled borders. Central ulceration may occur, and the lesions may enlarge to several centimeters in diameter. They may grow slowly or even remain stationary for several years. Malignant transformation is usually indicated when either ulceration or papillomatous proliferation occurs. Microscopically, there is interpapillary acanthosis with long, narrow rete pegs and hypoplastic stra-

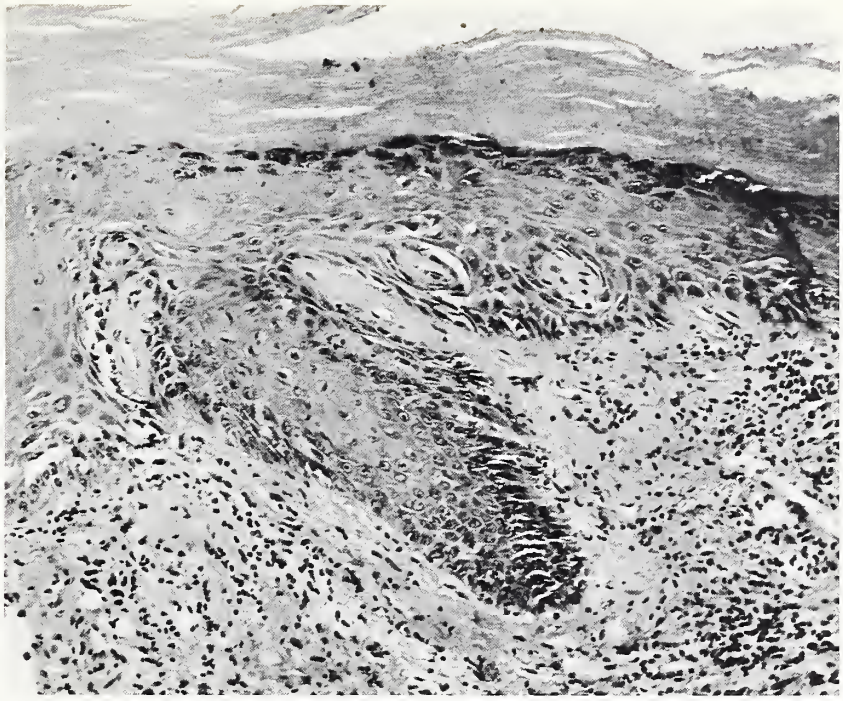

Figure 115. Leukoplakia. This lesion is characterized by marked hyperkeratosis, acanthosis, and chronic inflammation of dermis. × 145. A. F. I. P. Acc. No. 218716–16.

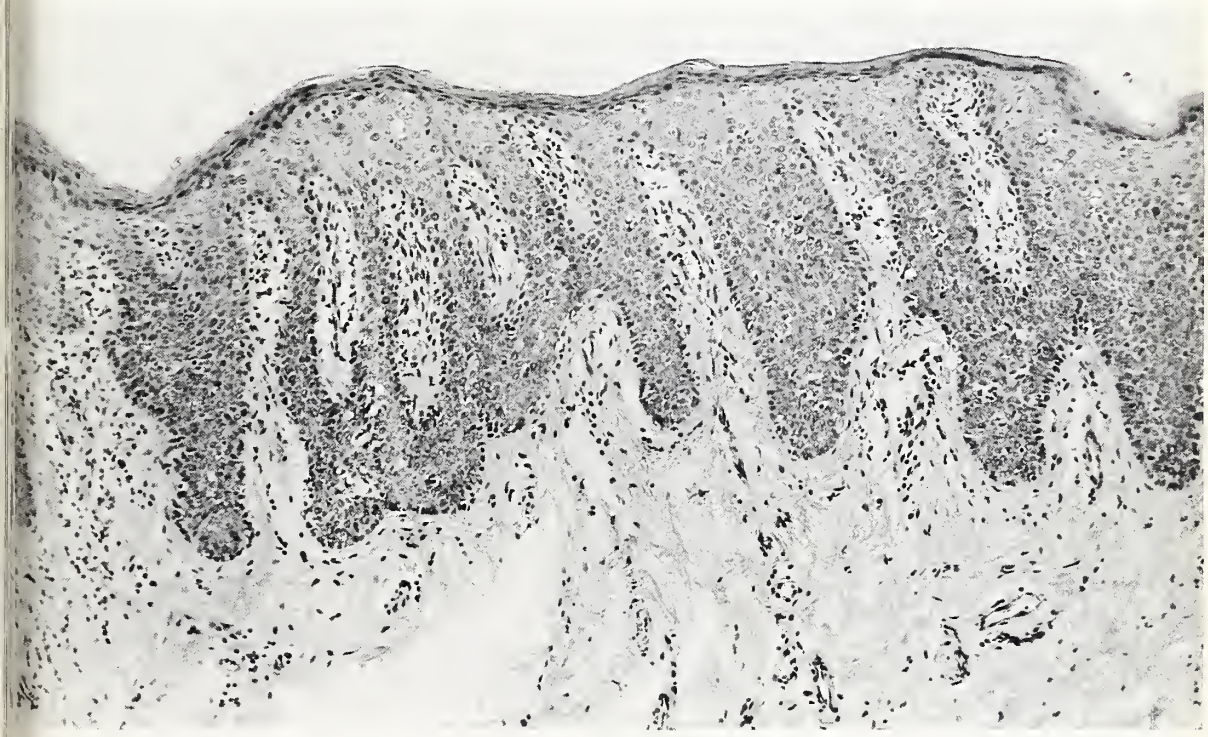

Figure 116. Erythroplasia of Queyrat. Note elongated rete pegs and hypoplasia of stratum corneum and granulosum. Mild inflammatory exudate is found in superficial dermis. × 100. (From the Armed Forces Institute of Pathology.) A. F. I. P. Acc. No. 117743–3.

tum corneum and stratum granulosum. The epithelial cells are either spindle-shaped or oval and relatively uniform in size. There are mitotic figures in all layers of the epithelium. The epithelial cells do not, however, show the anaplasia and disorganization characteristic of neoplasia. The underlying cutis is infiltrated by plasma cells, lymphocytes, and polymorphonuclear cells and contains an increased number of capillaries (figs. 116–118).

Carcinoma in situ, or Bowen's disease, shows all the morphologic changes characteristic of neoplasia except invasion. Whether these lesions always develop into invasive carcinoma is disputed, but it is certain that a large number of them do become invasive in time. Carcinoma in situ may develop almost anywhere in the skin or mucous membrane. On the glans penis it develops as a well defined papulosquamous plaque or macule with a red, scaly, or ulcerated surface, and often it grossly resembles erythroplasia. Microscopically, the epithelium shows carcinomatous hyperplasia with marked cellular anaplasia and dyskeratosis. Mitoses, some of which may be atypical, and single keratinized cells may be found in all layers of the epithelium. Bizarre multinucleated tumor cells are frequently present. There is a variable amount of intercellular and intracellular edema of the epithelium (figs. 119, 120).

Epidermoid Carcinoma

SYNONYMS AND RELATED TERMS: Squamous cell carcinoma.

DEFINITION. Malignant epithelial tumors which arise from the skin of the penis.

INCIDENCE AND ETIOLOGY. Epidermoid carcinoma of the penis is limited almost entirely to the uncircumcised or to those circumcised after the early years of life. Its incidence thus varies in different parts of the world according to the prevailing social and religious customs affecting circumcision. Penile carcinoma comprises only from 1 to 3 percent of all malignant tumors in the male in the United States and Europe in contrast to 18 percent in the Orient. In the United States patients are usually between 40 and 70 years of age, while in the Orient their age averages 10 years less (Ngai). According to Hebrew ritual, circumcision is performed within the first two or three weeks of life and, with a single exception, no Jew so circumcised has been reported to have carcinoma of the penis. The exception was a carcinoma which occurred in a badly scarred wound resulting from cautery of a venereal lesion. Mohammedan circumcision is performed from the third to the tenth year of life or even later, and among Mohammedans penile carcinoma rarely occurs. Of more than 2,500 cases reported in the literature, only 33 occurred in men circumcised in the early years of life (Wolbarst).

Two other conditions commonly associated with penile carcinoma and probably of primary importance in its genesis are phimosis and balanitis (present in from 50 to 99 percent of reported series). The result of these con-

Fig. 117

Figure 117. Erythroplasia of Queyrat. Epithelial hyperplasia and inflammatory exudate more conspicuous than in figure 116. This was taken from an ulcerated lesion. × 75. (From the Armed Forces Institute of Pathology.) A. F. I. P. Acc. No. 155299–4.

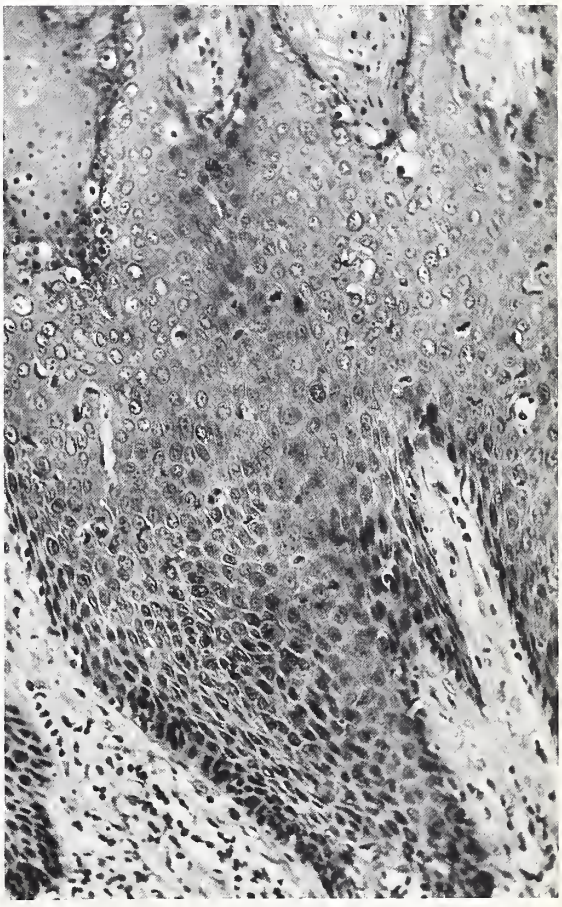

Fig. 118

Figure 118. Higher power of lesion illustrated in figure 117. Epithelial cells lack anaplasia of malignant growth and are frequently spindle-shaped. Mitotic figures are abundant. × 210. (From the Armed Forces Institute of Pathology.) A. F. I. P. Acc. No. 155299–3.

ditions is the retention of smegma and products of inflammation, causing both chemical and mechanical irritation of the glans and inner surface of the prepuce, where the majority of carcinomas arise. The fact that carcinoma of the penis has never been found in those circumcised in the first weeks of life, but occasionally occurs in those circumcised between the third and tenth years, would indicate that the irritation of the preputial cavity must begin in the early years of life.

It is interesting that, unlike scrotal carcinoma, penile carcinoma bears no relationship to occupational exposure; yet the contact with carcinogenic agents must be virtually identical for both scrotum and penis. There is a somewhat higher incidence of syphilis in men with penile carcinoma than in the general male population. Syphilitics who develop carcinoma of the penis do so from 10 to 20 years earlier than nonsyphilitics.

COURSE. In spite of the frequent handling and observation of the penis, penile carcinomas do not cause patients to seek treatment early. Fourteen months to two years is the average duration between onset of symptoms and diagnosis and treatment. Perhaps social stigma accounts for some of this delay in reporting; certainly the frequent phimosis and associated inflammation conceal or mask many early neoplasms.

The carcinoma first appears as a small ulcer, pimple, or wartlike lesion. If retraction of the prepuce is impossible, the first signs are itching or burning, a foul discharge which may be blood-tinged, presence of a lump palpable through the prepuce or, less frequently, pain, hemorrhage, and interference with urination.

As the lesion develops, ulceration and inflammation are the rule. The inguinal nodes are frequently enlarged because of inflammation in half the cases and metastatic carcinoma in the remainder. About 30 percent of all patients have inguinal metastases at first clinical examination.

PROGNOSIS. The survival and cure rates of these tumors vary somewhat with different methods of treatment. Surgical amputation of part or all of the penis with dissection of regional nodes when indicated is generally accepted as the treatment of choice. With such therapy the prognosis is relatively good when regional metastases are not present. In a series of 63 patients without metastases, reported by Barringer, 55 lived from one to 10 years after surgery without recurrence. Late recurrences are infrequent. Prognosis when metastases are present is much poorer. Barringer reports only two 5–year survivals in 37 such patients. With node dissection, Taylor and Nathanson report 42 percent 3–year survivals.

There is a slight, but not striking, correlation between the microscopic grades of malignancy and survival of patients.

GROSS. Carcinoma of the penis occurs most commonly in the coronal

Figure 119. Carcinoma in situ or Bowen's disease of penis. Normal skin at top of picture can be contrasted with thickened, anaplastic carcinomatous epithelium. Although the malignant epithelium is thickened, there is no break-through of the basement membrane with frank invasion. × 145. (From the Armed Forces Institute of Pathology.) A. F. I. P. Acc. No. 83806–3.

Figure 120. High power view of carcinoma in situ shown in figure 119. Complete obliteration of normal epidermal strata. Anaplasia and dyskeratosis are apparent. Giant cells and mitoses are frequent. × 315. (From the Armed Forces Institute of Pathology.) A. F. I. P. Acc. No. 83806–2.

Fig. 119

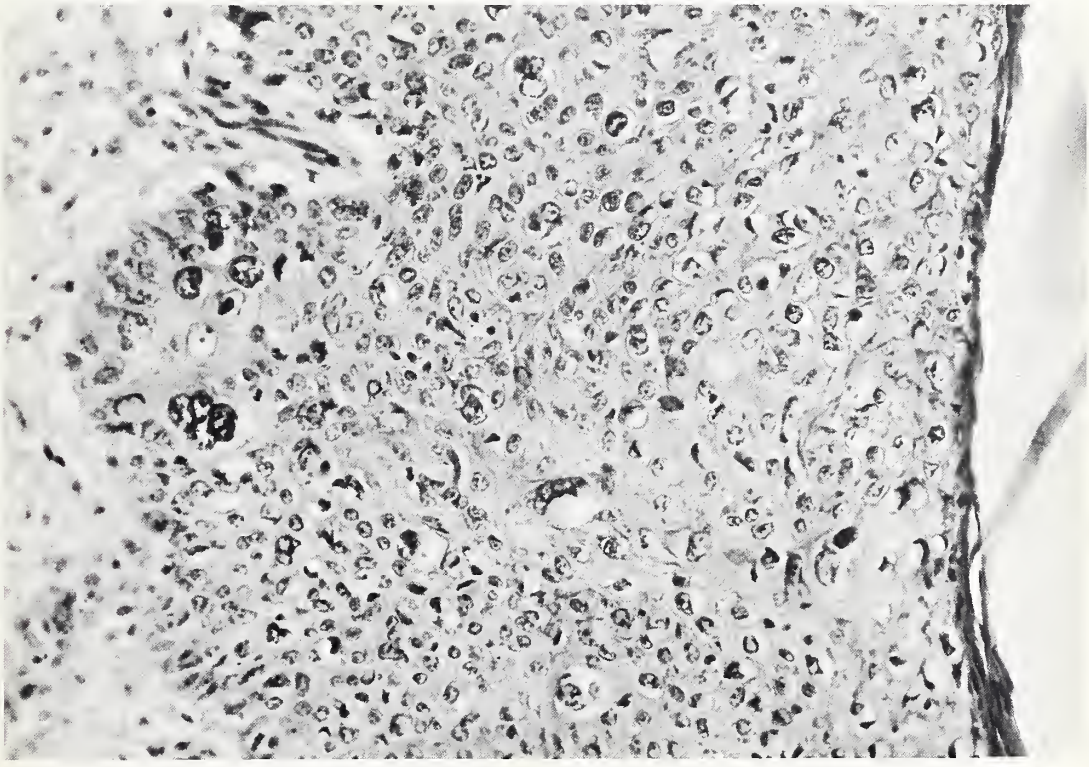

Fig. 120

Figure 121.* Externally visible nodule arises from carcinoma of inner layer of prepuce. Phimosis and balanitis usually associated with penile carcinoma are evident. A. F. I. P. Acc. No. 130209–1.

Figure 122.* Low grade papillary epidermoid carcinoma of the penis. Infiltration of dermis by large masses of relatively well differentiated epithelium bespeaks its low malignancy. × 20. A. F. I. P. Acc. No. 218716–20.

Figure 123. Sagittal section of penis widely infiltrated by carcinoma. Point of origin was apparently inner prepuce and coronal sulcus. White tumor can be seen infiltrating much of glans and extending into shaft. A. F. I. P. Acc. No. 181207–3.

*From the Armed Forces Institute of Pathology.

Fig. 121

Fig. 122

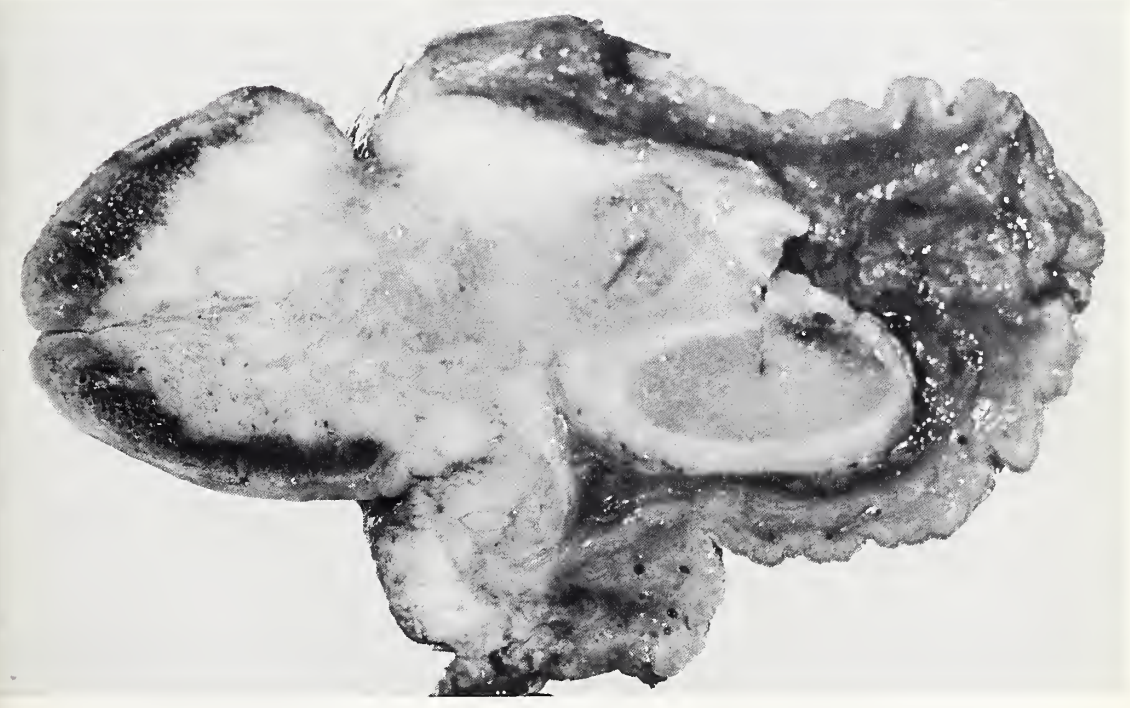

Fig. 123

Figure 124.* Infiltrating penile carcinoma. Junction of acanthotic non-neoplastic epithelium on left with undifferentiated invasive tumor on right is striking. Surface of tumor is ulcerated. × 76. A. F. I. P. Acc. No. 184292–3.

Figure 125.* High power view of infiltrating margin of tumor seen in figure 124. Anaplastic tumor cells are predominantly spindle-shaped, show considerable mitotic activity, and little keratinization. There is active infiltration of tumor cells into inflammatory dermis. × 340. A. F. I. P. Acc. No. 184292–4.

*From the Armed Forces Institute of Pathology.

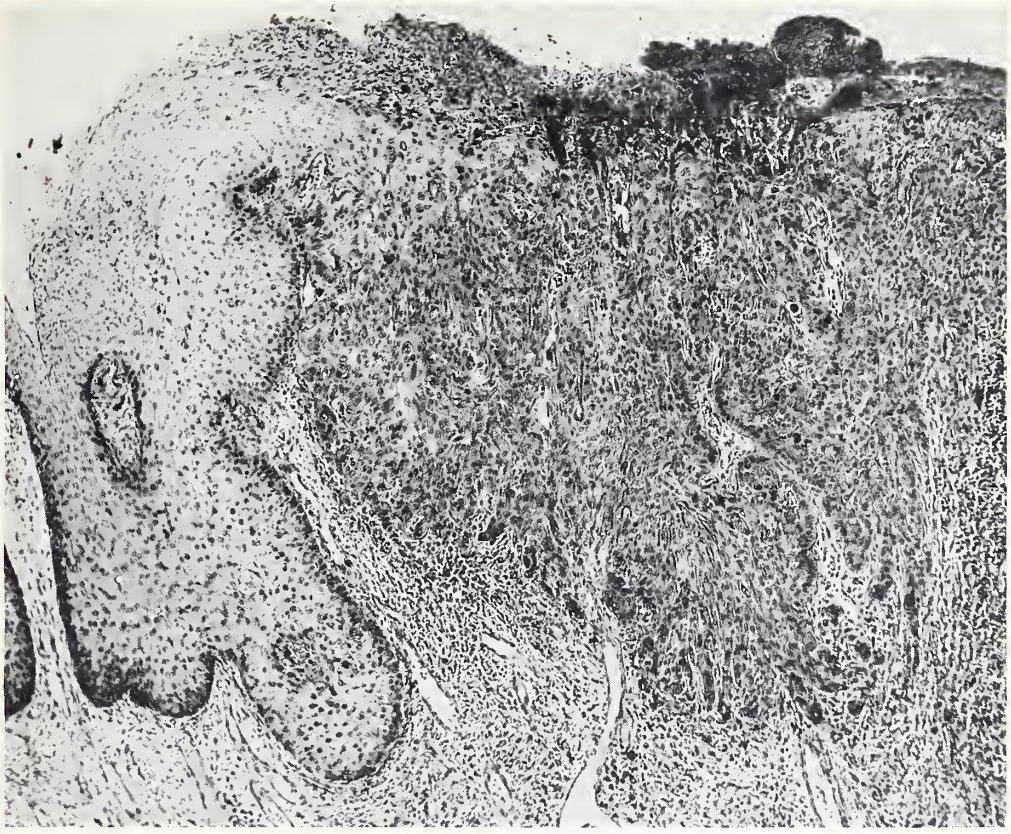

Fig. 124

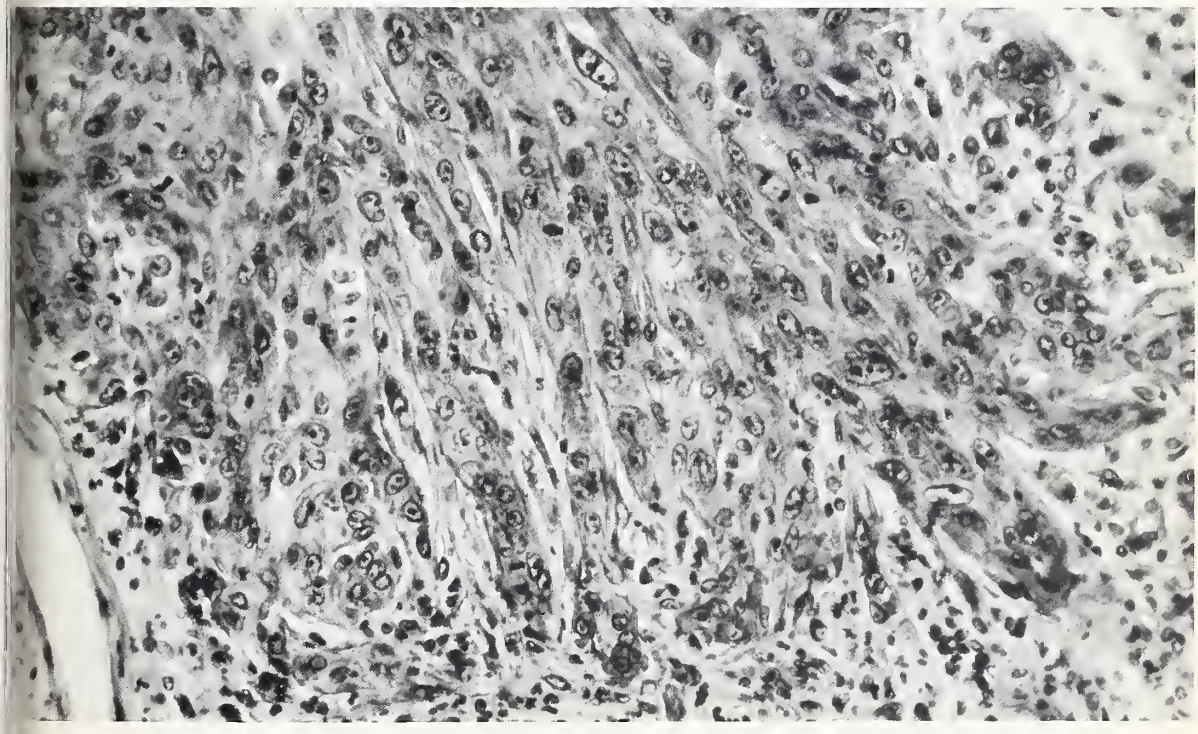

Fig. 125

sulcus or the proximal third of the glans or prepuce and only occasionally on the skin of the shaft. Characteristically, these tumors are either papillary or infiltrating, with a slight preponderance of the latter (figs. 121, 123).

The papillary tumors usually begin as warts on the glans or inner surface of the prepuce. They later form irregular fungating masses which may penetrate and destroy the prepuce. Ulceration usually occurs before the tumors become large. Infection follows ulceration and causes induration, purulent discharge, and occasional bleeding.

The infiltrative tumors begin as smooth, slightly raised, indurated, red lesions. Frequently, central superficial ulcers with slightly rolled edges and irregular necrotic bases develop and are occasionally mistaken for chancres. These tumors infiltrate the skin widely and become fixed to the underlying tissues. The rate of growth as indicated by the diameter of tumors of both types is about the same.

Buck's fascia prevents tumor invasion of the corpora cavernosa until relatively late in the course of the disease, but after invasion of the cavernous erectile tissue the tumor spreads rapidly. There is only late involvement of the urethra.

MICROSCOPIC. Penile carcinoma is usually well differentiated epidermoid type, the cells of which demonstrate keratinization and "pearl" formation, slight to moderate mitotic activity, and well formed intercellular bridges. Various series report from 60 to 73 percent of these tumors in the lower grades of malignancy. In papillary growths, the important features are papillary proliferations and limited invasion by tumor cells. These cells are large, polygonal, frequently well keratinized and well differentiated, and form irregular, infiltrating masses. The infiltrative tumors tend to be less well differentiated and show more atypical cells and mitoses. They are more invasive than the papillary type and tend to grow as small islands of tumor cells widely infiltrating the subcutaneous tissues (figs. 122, 124, 125).

The tumor invasion does not usually penetrate the fibrous capsules of the corpora spongiosa, but not infrequently involves lymphatics and occasionally blood vessels.

Surface ulceration of either type occurs early and is followed by chronic inflammation.

METASTASES. As previously mentioned, about 30 percent of penile carcinomas have metastasized at the time of diagnosis. Metastases are found in three groups of regional lymph nodes: the superficial inguinal, the deep inguinal, and the external iliac. Gross classification of penile carcinomas is of value in predicting the occurrence of metastases. Papillary tumors rarely metastasize (2 of 112 such tumors reported by Demarquay), while infiltrative tumors do so readily. Ngai reports a greater incidence of metastases in the carcinomas microscopically graded as highly malignant.

Distant metastases occur occasionally and are late manifestations found in about 15 percent of autopsied cases.

Miscellaneous Malignant Tumors

Miscellaneous malignant penile tumors include Paget's disease, basal cell carcinoma, sarcoma, melanoma, endothelioma, and metastatic tumors.

Extramammary Paget's disease is uncommon. A few instances in the penis have been described arising in the Fordyce glands and extending into the epithelium of the glans or coronal sulcus. The microscopic picture is identical with Paget's disease in the breast. In both the ducts of the glands and the deep layers of surface epithelium there are large, round, hydropic, epithelial cells with hyperchromatic nuclei, the Paget cells (Melicow and Ganem).

Two **basal cell carcinomas** of the penis have been reported.

Primary **sarcomas** have been reported under a variety of descriptive terms. A review of fibrosarcomas in 1944 revealed eight cases in the literature (Wattenberg). In 1924 Joelson reviewed all primary sarcomas of the penis and found, in addition to fibrosarcoma: 2 spindle cell sarcomas, 4 mixed cell sarcomas, 7 round cell sarcomas, and 2 unclassified sarcomas. Of these tumors, three were in patients under 10 years of age, four in young adults, and the remainder in the usual tumor age group.

Eleven malignant **melanomas** have been reported in men from 48 to 72 years of age. The malignancy of these tumors varied greatly.

Seven **endotheliomas** arising from the lining cells of the vascular spaces of the corpora cavernosa and exhibiting chiefly intravascular growth have been described. Three were highly malignant tumors and four were slow-growing.

Twenty cases of carcinoma metastatic to the penis have been described, with location of the primary tumor as follows: bladder 5, prostate 4, testis 3, kidney 3, rectum 3, lung 1, and liver 1. These metastases may cause priapism or urinary obstruction (Wattenberg).

Tumor-like Lesions

Condylomata acuminata are papillary or wartlike growths occurring singly or in crops most frequently on the penis, occasionally elsewhere in the genital region, and rarely in other parts of the body. They may occasionally be mistaken for carcinomas. Although some dispute still exists, most workers agree that the condylomata acuminata are caused by a filtrable virus, with trauma and contact with inflammatory exudates acting as inciting factors (Eller). On the penis these lesions occur most frequently in the coronal sulcus, posterior edge of the glans, and inner surface of the prepuce. They may be sessile or pedunculated, nodular or papillary, and red or purple. In some instances condylomata reach several centimeters in diameter and are cauli-

flower, raspberry, or cockscomb in shape. When dry, the surface is well keratinized, but when moist, it is usually macerated.

The histologic characteristics include a circumscribed thickening of the epithelium caused by a proliferation of the squamous cell layer, a hyperplasia of rete pegs, and an increased mitotic activity of cells not only in the basal layer, but also in the squamous layer. The papillary processes of the dermis are vascular and contain a cellular infiltrate. Although the epithelium may show marked proliferation and numerous mitoses, the absence of anaplasia and invasion in condylomatas should distinguish them from carcinomas (fig. 126).

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Figure 126. Condyloma acuminata of penis. Active epithelial growth, marked thickening of squamous cell layer of epithelium, and hyperplasia of rete pegs are characteristic. There is absence of anaplasia and infiltration. × 12. (From Friedman, N.B., and Ash, J. E. Atlas of Genitourinary Pathology. Washington, D. C.: American Registry of Pathology, 1946.) A. F. I. P. Acc. No. 130846.

TUMORS OF THE SCROTUM

Introduction

The scrotum is made up of specialized skin and subcutaneous tissue. The skin is pigmented, has well developed sebaceous and sudoriparous glands, and a furrowed surface. The furrowing of the skin is caused by contraction of a layer of smooth muscle fibers in the deep part of the dermis, the dartos. Beneath the dartos is a layer of laminated connective tissue, internal to which are located scattered bundles of the striated cremaster muscle. The scrotum is richly supplied with blood vessels and lymphatics. The lymphatics drain into the superficial inguinal lymph nodes.

Tumors arise most commonly from the epidermis and less frequently from the various connective tissue elements of dermis and subcutaneous tissue.

Epidermoid Carcinoma

SYNONYMS AND RELATED TERMS: Chimney sweep's cancer; Kangri cancer of skin; mule spinner's cancer; squamous cell carcinoma.

DEFINITION. A malignant tumor which arises from the epithelium of the scrotum.

ETIOLOGY. Most carcinomas of the scrotum result from exposure, usually occupational, to various carcinogens. In 1832 cancer of the scrotum was first described and became known as "chimney sweep's cancer" because of the frequent association of this tumor with the sweep's exposure to soot. Legislation has improved the sweep's working conditions, reducing this source of tumors by now to one of historic interest. However, many new occupational hazards have appeared which, while not as potent in the initiation of scrotal carcinomas as the soot tars to which the sweeps were exposed, nevertheless cause most of these tumors today. Mule spinners' exposure to machine oil, paraffin press workers' exposure to paraffin and other petroleum fractions, and the exposure of other workers to pitch, creosote, tar, and petroleum products are foremost among the occupational hazards (fig. 127). In addition to these occupational carcinogenic agents, medication with coal tar ointments and arsenic preparations occasionally results in scrotal carcinomas.

The remaining scrotal carcinomas, those with no demonstrable carcinogenic exposure, are apparently determined by social and economic factors. In contrast to carcinoma of the penis, which is uniformly distributed among the various social classes, carcinoma of the scrotum is most commonly found among the poor, the less clean city dwellers, and the industrial laborers, while it is almost nonexistent in unindustrialized countries. Thus, it appears that virtually all scrotal carcinomas result either from exposure to known carcinogens or from unclean urban living conditions (Kennaway and Ken-

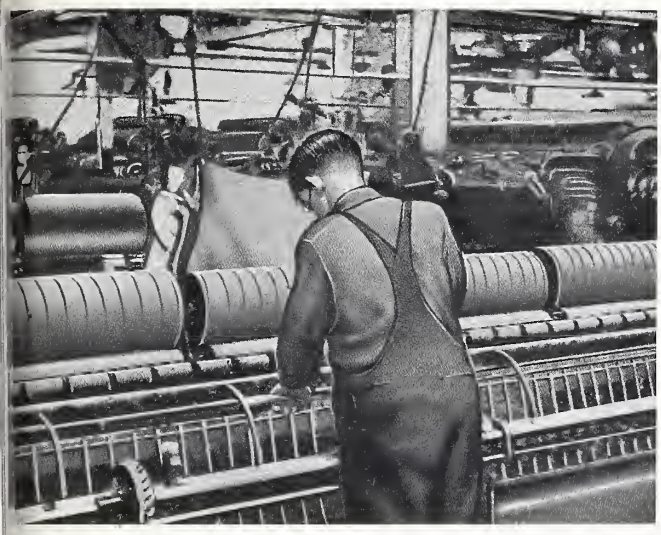

Fig. 127

Figure 127.* Mule spinner. Oil from machinery in front of spinner saturates area of clothing over the genital region. Carcinoma of the scrotum is found frequently in these workers. A. F. I. P. Acc. No. 218716–4.

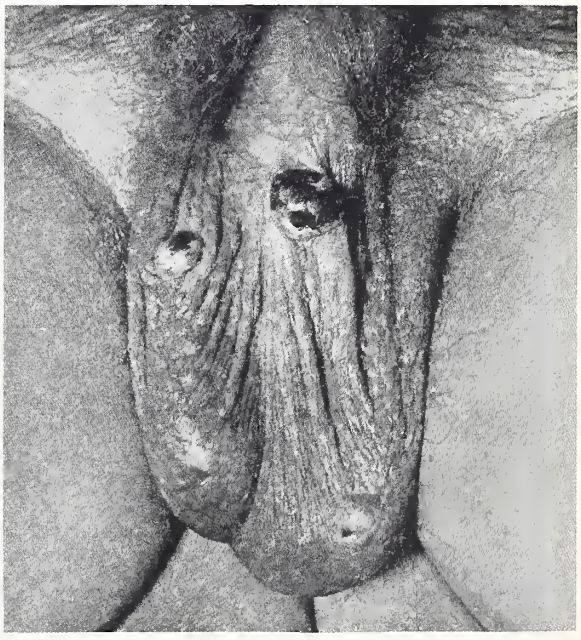

Fig. 128

Figure 128.* Carcinoma of scrotum at junction of scrotum with penis. A smaller second lesion is seen on right scrotum. The patient was a corkstone maker, aged 65. A. F. I. P. Acc. No. 218716–5.

*From Henry, S. A. Cancer of the Scrotum in Relation to Occupation. London: Oxford University Press, 1946.

naway). It is possible that unclean urban existence could result in the prolonged contact of soot and similar substances with the scrotum which would, in some degree, simulate the exposure of the chimney sweep.

The carcinogenic stimulus responsible for the development of scrotal carcinoma is applied in most cases to the entire surface of the skin, or at least to a region much greater than the scrotum alone. Yet carcinoma develops in the scrotum much more frequently than in the rest of the skin (although there is a definite tendency for men with scrotal carcinoma to have other primary malignant tumors, especially of the skin). This indicates that the scrotal skin has a peculiar predisposition to cancer. Many attempts have been made to connect this peculiarity with the wrinkled skin surface, the numerous sebaceous glands, and the presence of frequently contracting dartos muscle, but none of the explanations is convincing. For the present this predisposition on the part of the scrotal skin to carcinogenesis must be recognized but unexplained.

COURSE. Scrotal carcinoma is seen most frequently in men between 50 and 70 years, with an average age of 65 years. There is usually a history of ten or more years' contact with a known carcinogenic agent (22 of 27 cases reported by Dean). Hyperkeratosis of the anterior or lateral scrotal skin commonly precedes the appearance of the carcinoma. The lesion at first is painless and grows slowly, attaining a diameter of approximately 2 cm. within six to 12 months, when medical aid is usually sought. About this time the lesion ulcerates, becomes painful, grows more rapidly, and has associated metastases in from one fourth to one half of the patients.

Resection of the primary tumor and dissection of the inguinal nodes frequently result in cures, even when inguinal metastases are present. The treatment of choice is surgical excision, since these tumors do not respond to roentgen therapy. Five-year survival rates vary from 30 percent (Dean) to 55 percent (Henry and Irvine), with much better prognosis for cases without inguinal metastases than for those with metastases. Frequently (in 30 percent of cases according to the report of Dean) scrotal carcinomas are coexistent with other primary malignant tumors.

GROSS. Carcinoma of the scrotum first appears as a wart, pimple, sore, or lump, most frequently in the skin over the anterior, lateral, or dependent portions of the scrotum. Later the tumor is discoid, fungates moderately, infiltrates locally, and has a hyperkeratotic surface until it ulcerates. The ulcerated surface becomes infected and covered with a purulent exudate. The margins of the lesion are raised and firm, even in the presence of extensive ulceration (fig. 128). The cut surface of the tumor is firm, white, and granular, with opaque white flecks of keratinized tumor cells.

MICROSCOPIC. Almost all of these tumors are moderately well differentiated epidermoid carcinomas, usually of low to moderate malignancy. On

the basis of histologic appearance, Dean classified a series of 27 cases as follows: 3 as grade I; 21 as grade II; 3 as grade III. The tumors are well keratinized, with pearl formation, numerous intercellular bridges, and slight to moderate mitotic activity (figs. 129, 130). There is local invasion of tissues and occasional invasion of lymphatics.

METASTASES. Metastases are not an early development. However, after a lapse of a year, the average time between appearance of the tumor and institution of treatment, from 25 to 50 percent of patients have inguinal metastases. Enlarged nodes containing metastatic tumor can usually be differentiated clinically from inflammatory nodes, which are also commonly associated with scrotal carcinoma. The nodes containing metastatic tumor are most often single, or few in number, and painless. The inflammatory nodes are numerous, relatively small, and painful. Metastatic spread beyond the inguinal nodes rarely occurs.

Miscellaneous Tumors

The miscellaneous tumors of the scrotum include nevi, the precise origin of which is still in question, and benign and malignant tumors arising from the smooth and striated muscle and fibrous tissue of the dermis and subcutaneous tissues (figs. 131–135).

Nevi occur occasionally on the scrotum and are said to be exclusively of the junctional type (fig. 131). The significance of junctional nevi is still in question. However, it has been claimed that junctional nevi, i. e., those with epithelial involvement, become malignant more frequently than those contained entirely within the dermis, and on that basis the prophylactic removal of scrotal nevi has been recommended (Allen).

Fibromas and **leiomyomas** occasionally arise in the scrotum. Grossly, they are similar to each other, usually small, ovoid, firm, discrete tumors, which have a glistening, gray-pink cut surface. Microscopically, the fibromas are composed of sheets and whorls of dense, often hyalinized, fibrous tissue. The leiomyomas have the characteristic pattern of interlacing bundles of spindle-shaped, smooth muscle cells.

Only rarely do sarcomas develop in the scrotum. A single **rhabdomyosarcoma** of the scrotum is among the two thousand tumors of the male genital system in the files of the Armed Forces Institute of Pathology. This tumor has the usual pleomorphic cellular pattern, with ribbon and banjo giant cells, and rare cells that show cross striations.

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Figure 129.* Epidermoid carcinoma of scrotum. Junction between non-neoplastic epithelium at top and invasive tumor is evident. Marked chronic inflammatory exudate in dermis is usual. × 100. A. F. I. P. Acc. No. 102675–9.

Figure 130.* Infiltrating margin of tumor seen in figure 129. Keratinization is marked, with a "pearl" seen near center of picture. There is considerable anaplasia, but only slight mitotic activity. × 205. A. F. I. P. Acc. No. 102675–8.

*From the Armed Forces Institute of Pathology.

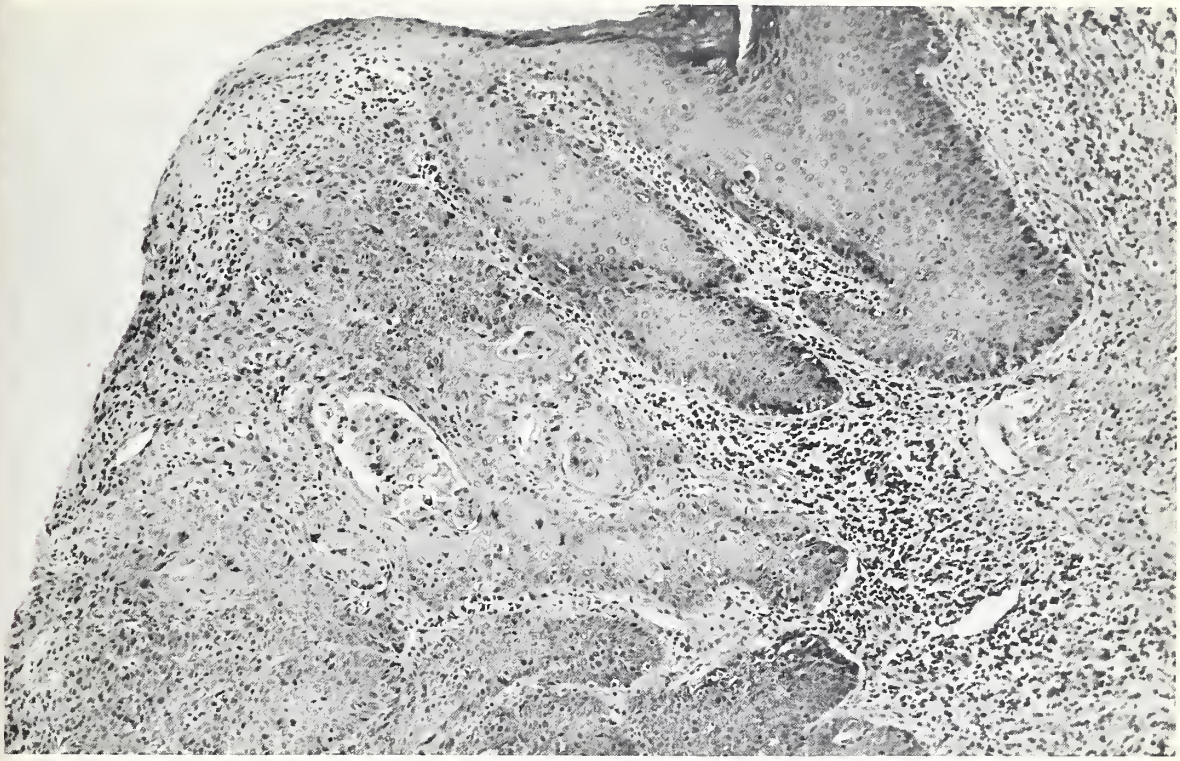

Fig. 129

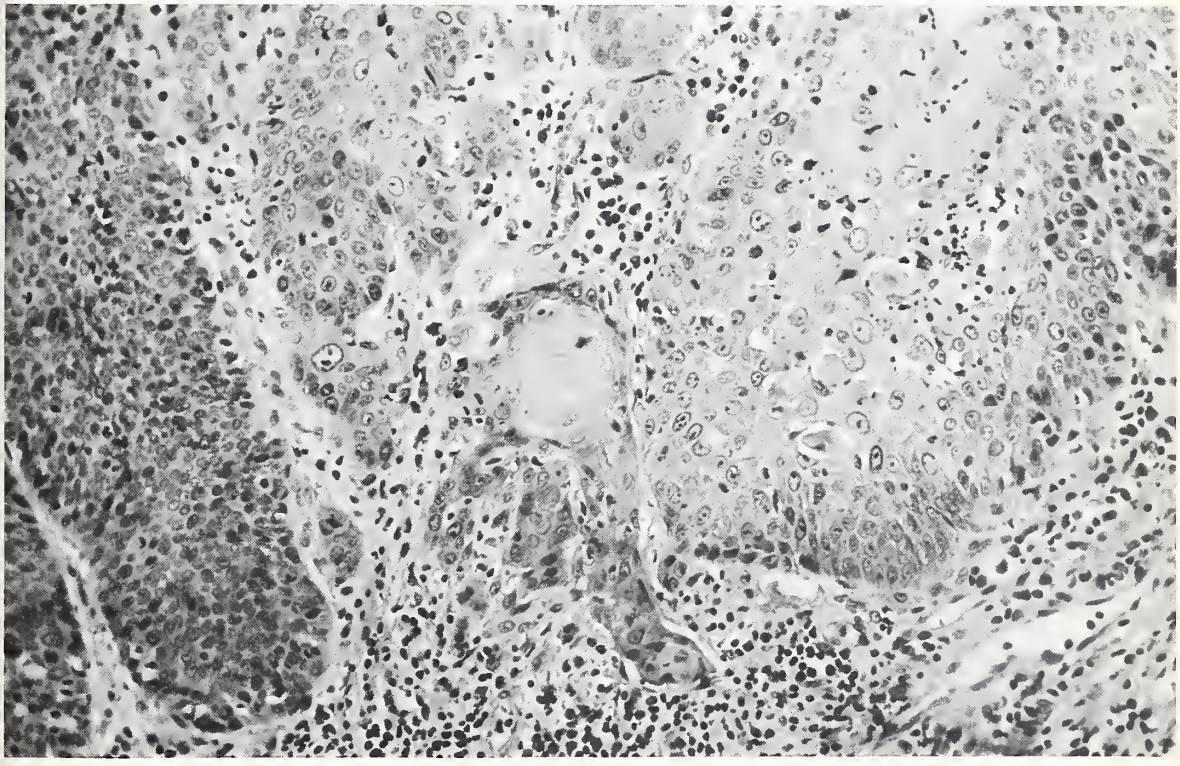

Fig. 130

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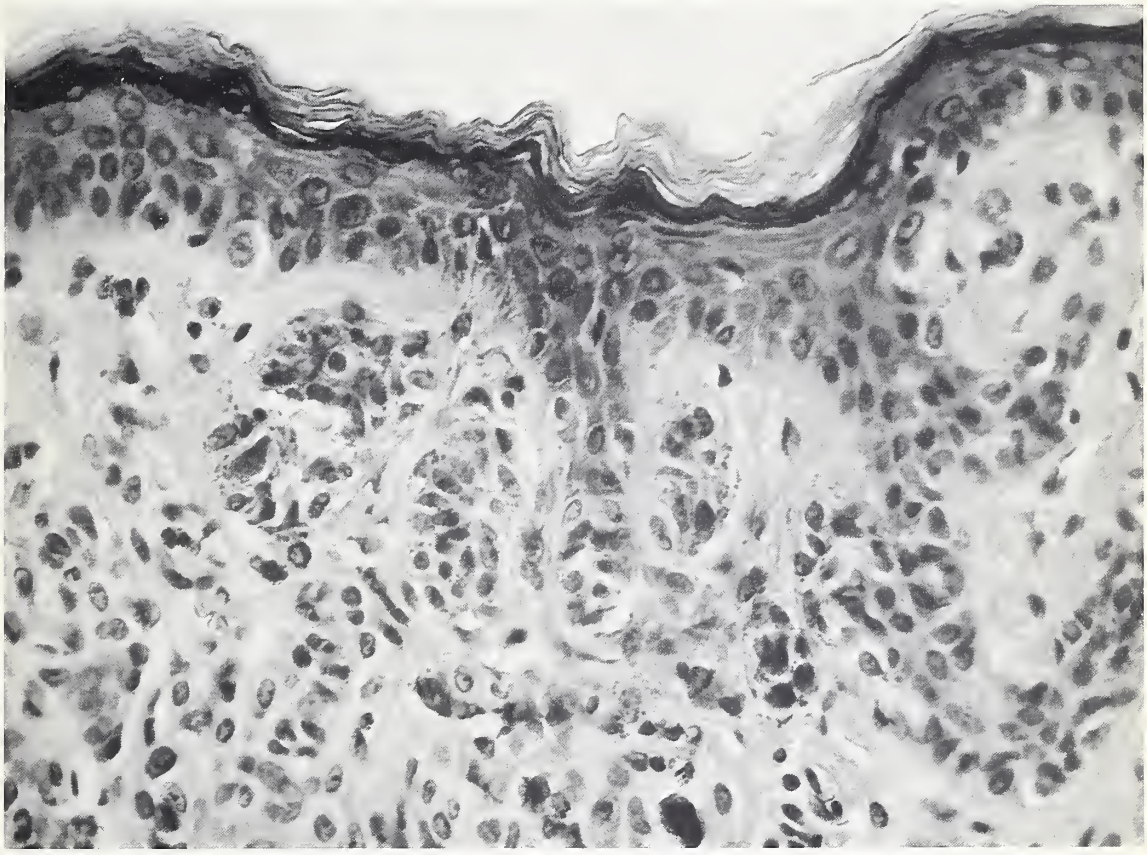

Figure 131. Junctional nevus of scrotum. Note nevus cells within epidermis, especially in the rete pegs. Fine pigment granules are present in and about many of the nevus cells. × 475. (From the Armed Forces Institute of Pathology.) A. F. I. P. Acc. No. 166202–1.

Figure 132.* Papilloma of scrotum. Benign lesion of proliferating epithelium. × 40. A. F. I. P. Acc. No. 173974.

Figure 133.* Epidermal inclusion cyst (so-called sebaceous cyst). This picture shows the true nature of these cysts, which arise from epidermis, although a point of connection between cyst wall and overlying epidermis can only occasionally be demonstrated. × 25. (From Friedman, N. B., and Ash, J. E. Atlas of Genitourinary Pathology. Washington, D.C.: American Registry of Pathology, 1946.) A. F. I. P. Acc. No. 90967.

Figure 134.* Hemangioma of scrotum. × 55. A. F. I. P. Acc. No. 218719.

Figure 135.* High power view of capillary hemangioma of scrotum. This benign lesion was well circumscribed and uniformly cellular with many small blood vessels throughout. × 395. A. F. I. P. Acc. No. 95576.

*From the Armed Forces Institute of Pathology.

Fig. 132

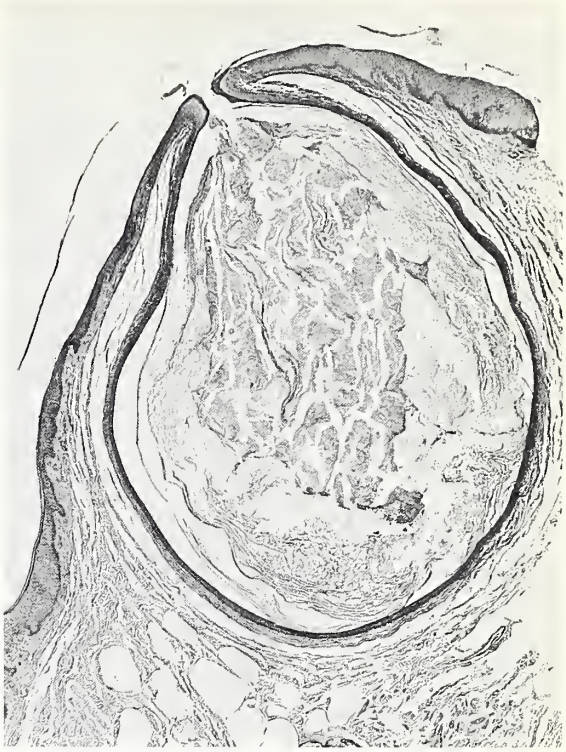

Fig. 133

Fig. 134

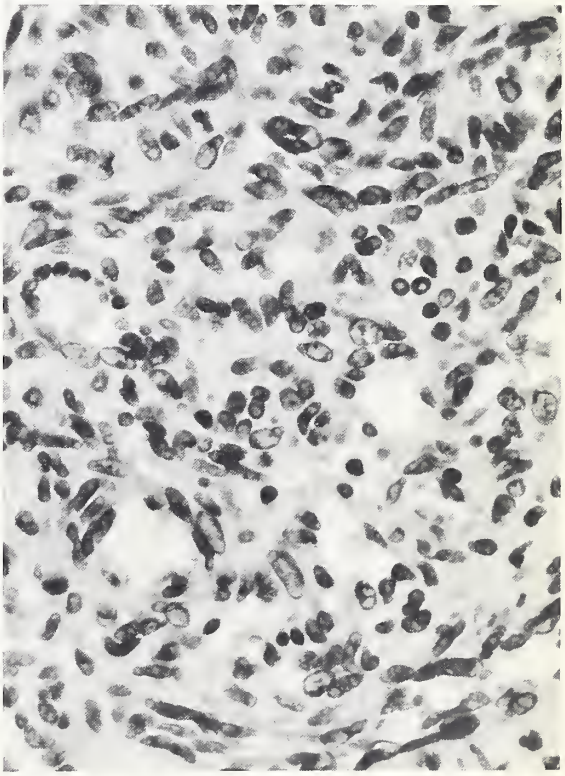

Fig. 135

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